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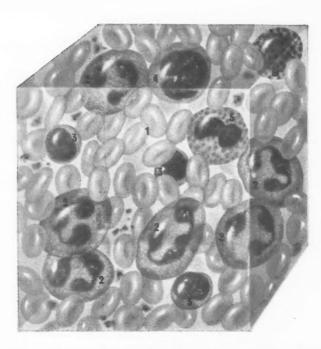
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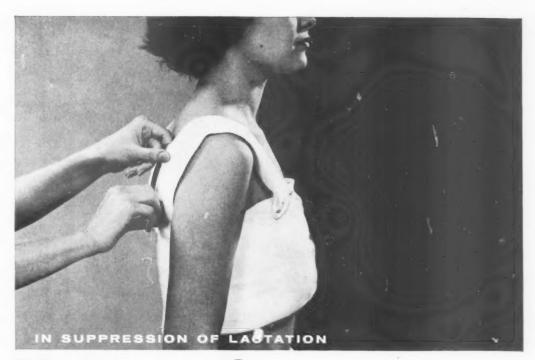
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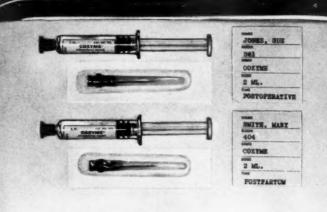
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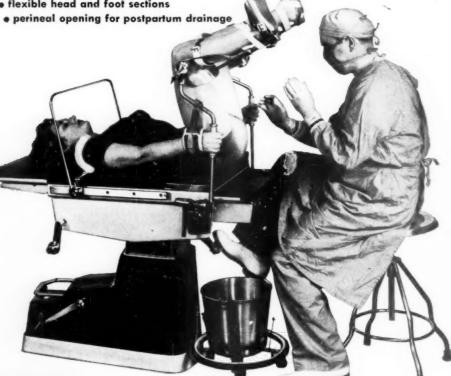
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The usual adult dosage is 2 Trancoprin tablets three or four times daily. The dosage for children from 5 to 12 years of age is 1 tablet three or four times daily. Trancoprin is so well tolerated that it may be taken on an empty stomach for quickest effect. The relief of symptoms is apparent in from fifteen to thirty minutes after administration and may last up to six hours or longer.

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Each Trancoprin tablet contains 300 mg. (5 grains) of acetylsalicylic acid and 50 mg. of chlormezanone [Trancopal® brand]. Bottles of 100 and 1000.

ODMIN Tablets / non-narcotic analgesic

References: 1. DeNyse, D. L.: M. Times 87:1512, Nov., 1959. 2. Ganz, S. E.: J. Indiana M. A. 52:1134, July, 1959. 3. Gruenberg, Friedrich: Current Therap. Res. 2:1, Jan., 1960. 4. Kearney, R. D.: Current Therap. Res. 2:127, April, 1960. 5. Lichtman, A. L.: Kentucky Acad. Gen. Pract. J. 4:28, Oct., 1958. 6. Mullin, W. G., and Epifano, Leonard: Am. Pract. & Digest Treat. 10:1743, Oct., 1959. 7. Shanaphy, J. F.: Current Therap. Res. 1:59, Oct., 1959. 8. Collective Study, Department of Medical Research, Winthrop Laboratories. 9. Hergesheimer, L. H.: An evaluation of a muscle relaxant (Trancopal) alone and with aspirin (Trancoprin) in an industrial medical practice, Ibid.

Winthrop LABORATORIES, New York 18, N. Y.

Americaine



Recipe for relief

when patients complain of

post-episiotomy / tender hemorrhoids

Americaine Topical Anesthetic Aerosol relieves OB discomforts promptly, saves nursing time, and often prevents infection because it is both bactericidal and fungicidal.

for best results:

ask patients to observe these simple instructions . . .

- 1/ Dry area before making application.
- 2/ Hold dispenser 8-12 inches away from area to be sprayed.
- 3/ Hold Aerosol upright (never upside down).
- 4/ After application, wait 2-3 minutes before applying pad.

HIGHEST POTENCY IN TOPICAL ANESTHETICS—Contains 20% dissolved benzocaine and 0.1% benzethonium chlor de in bland, water-washable vehicle.

THERE IS A FREE AMERICAINE AEROSOL FOR YOU. Please enclose prescription blank when requesting.

3 HANDY SIZES:

3 oz. and 6 oz. for assignment to individual patients, 12 oz. for professional use and floor stock. ALSO: Americaine Ointment—Same potent formula—in 1 oz. tubes.

Americaine®

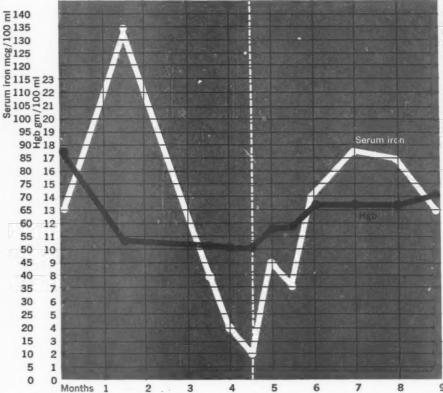
TOPICAL

AEROSOL

ARNAR-STONE LABORATORIES INC. / MT. PROSPECT ILLINOIS

When is his hemoglobin normal?

the case of infant #1854'



Male, healthy, one of a group fed an evaporated milk formula until four and one-half months of age. At this time, his serum iron had dropped below the acceptable 50 mcg/100 ml level to a low point of 10. Hemoglobin readings, while going down, followed the "nonanemic pattern for this age and never went below 10 gm/100 ml.

This infant's feeding was then changed to Similac With Iron, which gives 12 mg of ferrous iron at spaced intervals with each quart of feeding. Within two weeks, serum iron was well above the pre-Similac With Iron level. Hemoglobin (and hematocrit) rose concomitantly and consistently.

Hemoglobin is usually the last of the blood indices to reflect iron status. "Previous investigations have indicated that [iron stores] must be depleted before iron deficiency becomes manifest in the circulating red cell mass. The depletion of iron stores associated with normal hematological measurements may therefore be regarded as the 'preclinical' phase of iron deficiency." And a strictly "normal" hemoglobin might be said to be that which is supported by optimal levels of serum iron.

Serum iron, hemoglobin and hematocrit all remain higher for infants on Similac With Iron and iron deficiency does not develop.³

through bottle feeding, through cup feeding

SIMILAC WITH IRON

first year prophylaxis to prevent second year depletion

12 mg of ferrous iron per quart of feeding 1. Marsh, A. K.: Personal communication. 2. Haskins, D., et al.: J. Clin. Invest. 31:543, 1952. 3. Marsh, A. K., et al.: Pediatrics 24:404 (Sept.) 1959.



ROSS LABORATORIES Columbus 16, Ohio

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she's on TACE

"...the most satisfactory drug for use at delivery in the suppression of lactation."2

In over 3,000 patients studied, 1.3 only 3 cases of refilling were reported.

Withdrawal Bleeding Rare, 1.3 since TACE, stored in body fat. is released gradually, even after therapy is discontinued.

Dosage: 4 capsules daily for 7 days.

Supply: Capsules containing 12 mg, TACE.

References:
1. Bennett, E. T., and McCann, E. C.: J. Maine M. A. 45:225. 2. Eichner, E., et al.: Obst. & Gynec. 6:511. 3. Nulsen, R. O., et al.: Am. J. Obst. & Gynec. 65:1048.

THE WM. S. MERRELL COMPANY CINCINNATI, OHIO . ST. THOMAS, ONTARIO



relieve the symptoms of premenstrual tension

for EDEMA...CYCLEX provides the prompt diuresis of HYDRODIURIL for rapid reduction of weight gain, breast fullness, abdominal congestion

for MOOD-CHANGES...CYCLEX supplies the effective relief of meprobamate for nervousness, irritability, tension, nausea, malaise, insomnia

for GI DISTRESS...CYCLEX affords quickacting relief of nausea and bloating associated with premenstrual tension

SUPPLIED: Tablets, bottles of 100. Each tablet contains 25 mg. of HYDRODIURIL (hydrochlorothiazide) and 200 mg. of meprobamate.

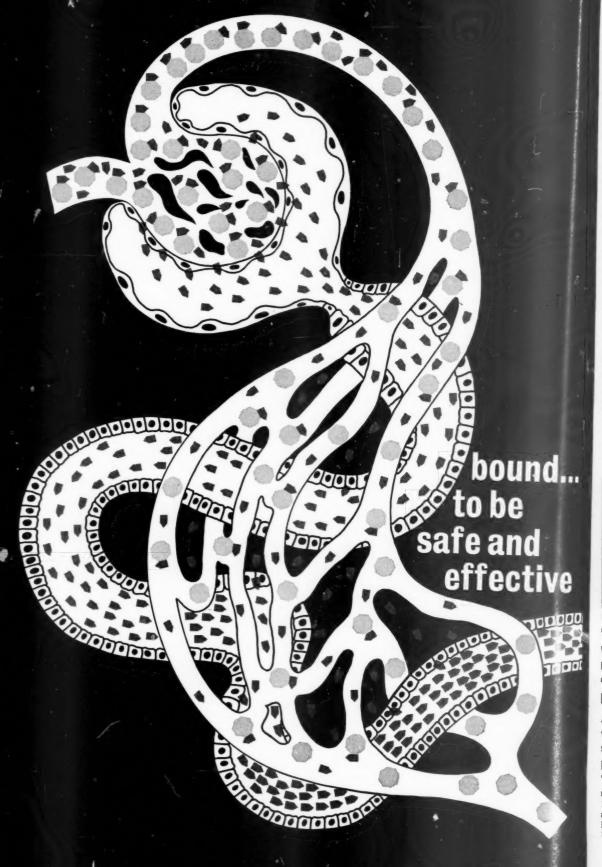
DOSAGE: Usual adult dosage is one tablet once or twice a day, beginning on the first morning of symptoms and continuing until the onset of menses. CYCLEX may be continued through the menstrual period.

Before prescribing or administering CYCLEX, the physician should consult detailed information on use accompanying package or available on request.

CYCLEX and HYDRODIURIL are trademarks of Merck & Co., INC.



MERCK SHARP & DOHME Division of Merck & Co., INC. West Point, Pa.



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195 2 al.: An M., Jr. ii any urinary tract infection: "it is the kidney which is the most important consideration"...
"Infections limited to the lower urinary tract are comparatively rare"."

In the bloodstream, free FURADANTIN and FURADANTIN bound to plasma proteins are in equilibrium free FURADANTIN passes readily through the glomerular filter. Protein-bound FURADANTIN, however, is not filtered by the glomerulus and reaches the peritubular capillaries. Here equilibrium is restored, and the FURADANTIN released from its bound state diffuses through the interstitial spaces and is secreted by the tubular cells. Exacting studies "suggest a three-component system for the renal transport of nitrofurantoin. That is, this nitrofuran appears to be filtered at the glomeruli and both secreted and reabsorbed by the tubules." 3

Furadantin safeguards the kidney via a "threecomponent system of renal transport" ... insuring continuous, intimate contact with functioning renal tissue

For more than 8 years . . . in over 8,000,000* courses of treatment . . . a distinguished record of safety and efficacy

FURADANTIN

bran of nitrofurantoin

"... may be given for extended periods of time without development of side effects or of drug-resistant mutants."

"... was given continuously and safely for as long as three years."

AVE LAGE FURADANTIN ADULT DOSAGE: 100 mg. tablet q.i.d.

with meals and with food or milk on retiring.

SUPPLIED: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg.

per 5 cc. tsp.

*Co servative estimate based on clinical use since introduction.

REFORENCES: 1. Thompson, I. M.: Family Physician, Chicago 9:14, 195°. 2. Campbell, M. F.: Mod. Med. 24:85, 1956. 3. Paul, M. F., et al.: Am. J. Physiol. 197:580, 1959. 4. Johnson, S. H., III, and Marshall, M., Jr.: J. Urol., Balt. 82:162, 1959. 5. Lippman. R. W., et al.: J. Urol., Balt. 80:77, 1958.



* EATON LABORATORIES

Division of The Norwich Pharmacal Company

NORWICH, NEW YORK

SAFE AND SOUND

IN ANY PREGNANC

to prevent morning sickness

With new Tigan 250 mg capsules you can now provide protection against morning sickness with only two capsules daily — one at bedtime and one in the morning. Tigan is so safe that it may be used with confidence as a routine prescription in any pregnancy. Avoiding the risks of phenothiazine derivatives and the limitations of the antihistamines, Tigan acts both therapeutically and prophylactically to stop active vomiting or to prevent nausea and vomiting.

Consult literature and dosage information, available on request, before prescribing.

TIGAN BIBLIOGRAPHY: 1. M. W. Goldberg, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 2. O. C. Brandman, ibid. 3. J. A. Lucinian and R. H. Bohn, ibid. 4. D. W. Molander, ibid. 5. B. I. Shnider and G. L. Gold, ibid. 6. W. S. Derrick, ibid. 7. B. Wolfson and F. F. Foldes, ibid. 8. L. McLaughlin, ibid. 9. W. K. Gauthier, Discussant, ibid. 10. H. E. Davis, Discussant, ibid. 11. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, J. Newark Beth Israel Hosp., 9:189, 1958. 12. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, J. Pharmacol. & Exper. Therap., 126:270, 1959. 13. W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, New York J. Med., 59:4217, 1959. 14. O. W. Doyle, Clin. Med., 7:43, 1960. 15. L. A. Nathan, Curr. Therap. Res., 2:6, 1960. 16. Council on Drugs, New and Nonofficial Drugs, J.A.M.A., 172:1038, 1960. 17. O. L. Davidson, J. Tennessee M.A., 53:140, 1960. 18. O. Brandman, Gastroenterology, 38:777, 1960. 19. B. A. Robin, Maryland M. J., in press. 20. A. L. Kolodny, Am. J. M. Sc., 239:682, 1960. 21. F. Cacace, Colorado GP, 2:5, 1960. 22. J. W. Bellville, I. D. J. Bross and W. S. Howland, Clin. Pharmacol. & Therap., TIGAN® Hydrochloride-4-(2-dimethylaminoethoxy). in press. N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride



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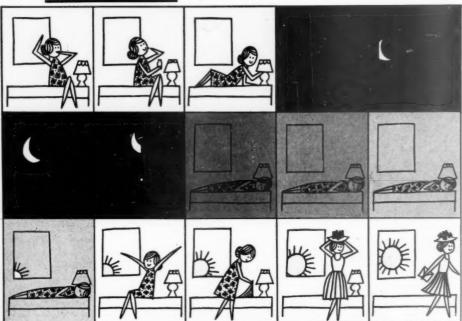
Division of Hoffmann-La Roche Inc.

San Scapsules

for faster, more prolonged, more effective antiemetic activity

BENDECTIN

at bedtime ?



prevents
morning sickness
here!

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"... I have gained the best results with [Bendectin]... Because these tablets have a protective coating...the dose taken at night becomes effective in the morning."

NEW DOUBLE-BLIND STUDY SHOWS BENDECTIN EFFECTIVE IN 94% OF PATIENTS²

Medication	Number of patients	Complete relief	Partial relief	Failure
Bendectin	52	23 (44%)	26 (50%)	3 (6%)
		TOTAL 94%		
Placebo	57	13 (23%)	24 (42%)	20 (35%)
		TOTAL 65%		

"Bendectin was administered in a preliminary study to 146 patients and later, in a controlled, double-blind study to 52 patients, or to a total of 198 patients suffering from nausea and vomiting of pregnancy. A very gratifying therapeutic response was obtained in 178 or 90 per cent. In a double-blind portion of this study, the response of 52 patients treated with Bendectin was compared with that of 57 other patients treated with a placebo. In this group of 109 patients, there was a favorable response to Bendectin in 94 per cent and to the placebo in only 65 per cent."2

Measure Bendectin against your present Rx:

- Q. Has your present Rx been shown to relieve morning sickness before it starts - in more than 9 out of 10 patients?2-5
- Q. Is your present Rx free of phenothiazine-like side effects and habituating properties?
- Q. Is it economical? Does it cost less per day, for example, than a quart of milk?

With Bendectin, the answer to all three is YES.

FORMULA:

Each white, specially coated tablet contains:

B ntyl (dicyclomine) hydrochloride 10 mg.

Decapryn (doxylamine) succinate 10 mg. Pyridoxine hydrochloride 10 mg.

DUSAGE: Two tablets at bedtime.

SUPPLY: Bottles of 100 and 500.

1. Middleton, T. F.: Postgrad. Med. 24:699, 1953.

2. Geiger, C. J., et al.: Obst. & Gynec. 5:688, 1959.

3. Nulsen, R. O.: Ohio State M, J. 53:665, 1957.

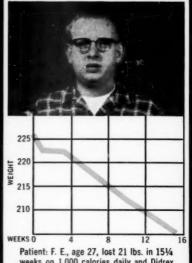
4. Personal communications, 1956-57.

5. Towne, J. E.: Internat, Rec. Med. 171: 583, 1958.

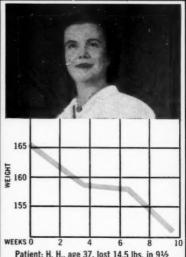
TRADEMARKS: BENDECTING, BENTYLE, DECAPRYNE



The Wm. S. Merrell Company Cincinnati, Ohio . St. Thomas, Ontario



Patient: F. E., age 27, lost 21 lbs. in 151/4 weeks on 1,000 calories daily and Didrex



Patient: H. H., age 37, lost 14.5 lbs. in 9½ weeks on 1,000 calories daily and Didrex



Patient: A. P., age 34, lost 18.5 lbs. in 11% weeks on 1,000 calories daily and Didra

Patient: L weeks on

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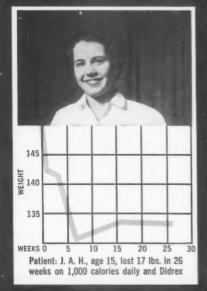
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UPJOHN ANNOUNCES









in obesity management Put it to your patient this way: The basic therapeutic objective of obesity management is to change dietary habits built over

months or years of weight accumulation. This takes time and will. Consider Didrex, the new Upjohn appetite suppressant. Happily, it elevates mood which makes dieting more acceptable. More important, it works: "persistent significant weight loss" in patients followed for as long as 20 weeks. Added to your favorite reducing regimen, ½ to 1 Didrex tablet one to three times daily is usually adequate to preclude the "weight plateau" that so often discourages dieters after a few weeks. Available as 50 mg. tablets in bottles of 100.

The Upjohn Company, Kalamazoo, Michigan

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride (+)-N-benzyl-N, α -dimethyl-phenethylamine hydrochloridel. A sympathomimetic compound with marked anorexic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of obesity.

Contraindications: None known, However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with 1/2 or 1 tablet (25 to 50 mg.) in midmorning for several days. Then adjust dosage to suit each patient's need to a maximum of 3 tablets daily (150 mg.). Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., press-coated, scored tablets, in bottles of 100.

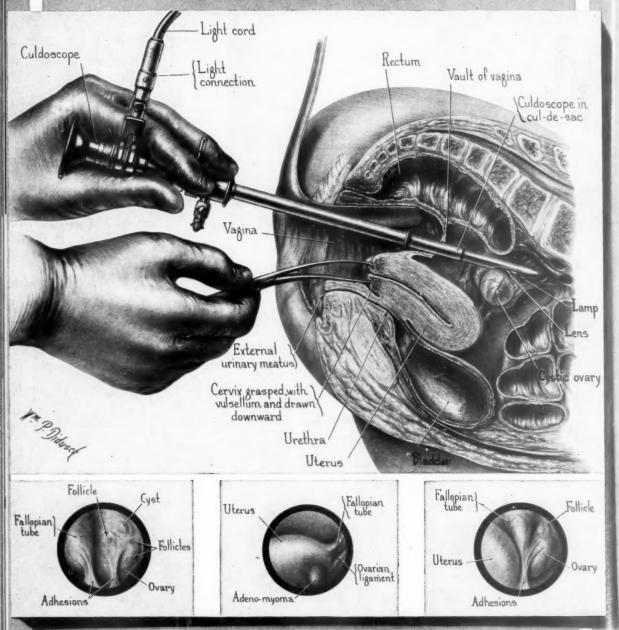
Photos and case histories courtesy Drs. Alan S. Rubenstein,

P.V. Dilts and William Conroy, Springfield, Illinois

*Trademark-brand of benzphetamine hydrochloride, UPJOHN

The Decker

CULDOSCOPE



The illustration above shows the Decker Culdoscope in endoscopic visualization of the female pelvic structures by the vaginal route. It permits direct study of pelvic tumors, ovarian pathologies, ectopic pregnancy, endometriosis, pelvic and intestinal adhesions, etc.

ESTABLISHED IN 1900



BY REINHOLD WAPPLER

FREDERICK J. WALLACE, President

American Cystoscope Makers, Inc.

8 PELHAM PARKWAY

PELHAM MANOR, N. Y.

Special Report from Mead Johnson and Company







- Corporate Objectives
- of
- Mead Johnson & Company
 - To earn an adequate return on invested capital through service in medicine.
 - To seek growth in the fields of specialty nutritional and pharmaceutical products.
 - To achieve growth through fundamental research and sound product development of the kind and quality designed to contribute to the advancement of medicine and the public welfare.
 - To provide adequate and trained management talent at all levels as required by the continuous needs of the business.
 - To provide formal training for all employees to promote individual growth and development.
 - 6. To maintain a high level of employee morale through continuous sound leadership and administration.
 - To discharge the obligation of corporate citizenship by effective participation in and contribution to industry, national, state and local affairs.

A Report to the Friends of Mead Johnson & Company

We are pleased to announce a new pattern of corporate organization, effective immediately. In order to enhance the Company's capability for service in medicine and to take advantage of the opportunities for growth in increasingly diversified fields of interest, the following autonomous divisions have been created.



Symbol of service in medicine

This Division will carry on the traditional business of Mead Johnson & Company under the following charter:

Mead Johnson Laboratories shall create and market medically validated nutritional and pharmaceutical products, including infant formulas and vitamins, for human use.

Mead Johnson Laboratories shall rely on fundamental research, applied research, and product development designed to contribute to the advancement of human health.

Mead Johnson Laboratories shall be guided by the following principles in support of its slogan, "Symbol of Service in Medicine":

- (a) To advance the practice of medicine as a science, by the dissemination of technical knowledge in specific fields of interest.
- (b) To contribute to formal medical education.
- (c) To contribute to essential research in medical institutions.
- (d) To provide a systematic program of medical practice aids.
- (e) To engage in programs designed to broaden public understanding of the proper role and function of the physician.

Mead Johnson Laboratories shall engage in a continuing program of clinical research to provide a rich background of clinical validation and support of its products.

Mead Johnson Laboratories shall promote its prescription products exclusively to the medical profession and pharmacists.

Mead Johnson Laboratories may, for specified non-prescription products, engage in medically approved point-of-sale promotion.

Mead Johnson Laboratories shall distribute its products exclusively through drug channels.



Quality products from nutritional research

A new Division, the Edward Dalton Company, is named in honor of Mead Johnson & Company's founder, Edward Mead Johnson, and his wife, Helena Dalton, who contributed significantly to the early success of the Company.

This new Division will operate according to the following charter:

The Edward Dalton Company shall create and market medically validated, special purpose nutritional products—other than infant formulas and vitamins.

The Edward Dalton Company shall rely on research and product development to achieve leadership through innovation.

The Edward Dalton Company shall be guided by these principles:

- (a) Clinical validation of all product claims.
- (b) Advertising and promotion that meet a high standard of integrity.
- (c) The creation of products of the type and kind which can be promoted for their assistance to and acceptance by physicians in their practice.

The Edward Dalton Company shall market its products:

- (a) By advertising and promoting both to physicians and the laity.
- (b) By the effective use of all necessary distribution channels.

(Metrecal^{T.M.}dietary for weight control has been assigned to this division.)



Symbol of service in medicine

This Division now functions in 85 countries throughout the world. Its charter is as follows:

Mead Johnson International shall develop, direct and expand the international operations of the corporation.

Mead Johnson International shall project world-wide the character, the principles and ethical posture of Mead Johnson & Company.

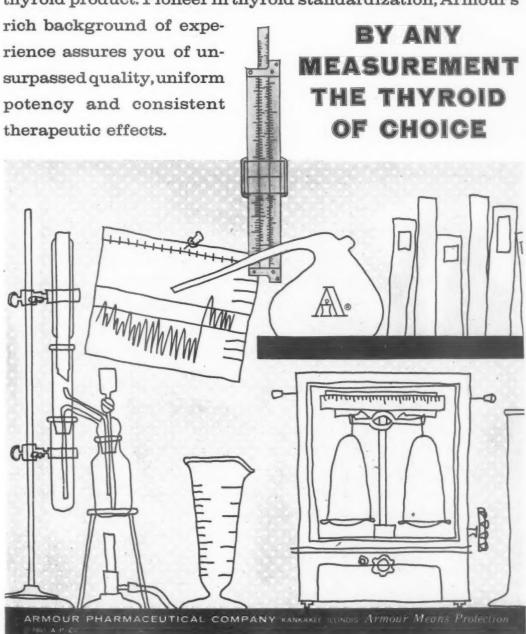
Mead Johnson & Company initiates this pattern of organization with confidence; with the conviction that the new structure will make it possible for the Company substantially to increase the scope of its contribution to the medical and allied professions and to the public.

Respectfully,

President

ALWAYS SPECIFY ARMOUR THYROID

ARMOUR THYROID for over half a century has been more widely prescribed...more widely dispensed than any other thyroid product. Pioneer in thyroid standardization, Armour's



announcing . .



new preanesthetic adjunctor

What Largon is

Injection Largon is a new phenothiazine derivative, generically 1-[10-(2-dimethy aminopropyl)phenothiazin-2-yl]-1-propanone hydrochloride.

What Largon does

LARGON is a potent sedative and adjunct to anesthesia and analgesia in obstetrics and in short-term surgery. It has a more rapid onset of action, with shorter duration and with fewer side effects than its predecessor, Phenergan® Hydrochloride (Promethaninima zine Hydrochloride, Wyeth). Its pharmacologic actions result in:

an antiemetic effect; enhancement of the effect of central nervous system depressants such as barbiturates, narcotics, anesthetics; and a sedative effect.

The predictable duration of its sedative effect is especially useful in short-term surger and in obstetrics. Largon in the recommended dose relieves apprehension and produce a light sleep from which the patient can be aroused easily.



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UPPL ARGON, ackages

no for obstetrics and short-term surgery

apid action . . . usually within less than 10 minutes by intramuscular injection, nmediately by intravenous injection.

nhancing action . . . on analgesics and anesthetics, thereby reducing considrably requirements for these agents. The resultant safety margin is wide.

hort predictable action . . . 3 to 4 hours—approximates that of meperidine nd allows repeat doses without overlapping effect; shortens recovery room time.

metha ninimal side action . . . significant maternal or fetal depression has not been eported, drug-induced jaundice or blood dyscrasias have not been observed, adverse ardiovascular effects have not been reported.

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ARGON, 20 mg. per cc. in Water for Injection U.S.P., is available in ampuls of 1 and 2 cc., oduce ackages of 25.

For further information on prescribing and administering LARGON, consult current Direction Circular enclosed with medication, or available on request.

> WYETH LABORATORIES / Philadelphia 1, Pa.

> > *propiomazine hydrochloride, Wyeth, Trademark

symptoms gone... feels like a new woman



basic therapy in vaginitis eliminates symptoms · itching · burning · leukorrhea · malodor · destroys pathogens · Trichomonas vaginalis · Candida (Monilia) albicans · nonspecific organisms...alone or in combination · has these advantages · high rates of clinical and cultural cures · effectiveness even in menstrual blood and vaginal debris · safe and nonirritating to delicate inflamed tissue · esthetically acceptable with no disagreeable staining

TRICOFURON®

Powder / Suppositories



 EATON LABORATORIES
 Division of The Norwich Pharmacal Company NORWICH, NEW YORK

A NEW PREPARED MILK FORMULA FOR MORE EFFICIENT NOURISHMENT

Looks and tastes like milk...offers nourishment comparable to that received by infants who are successfully breast fed. Immediately acceptable to the newborn, it helps the infant make an easy transition to fresh milk later.

Excellent protein and calorie utilization. A recent clinical study indicated that infants receiving Modilac, in general, performed more efficiently than those of the control groups; weight increment from 2 to 16 weeks was highest; weight gain per unit of protein or per calorie consumed was greatest.

Modilac is "flash-sterilized." Browning and caramelization, the result of aminosugar bonding and prolonged high processing temperatures, are markedly reduced. Destruction of heat-labile amino acids and vitamins is minimized.

The carbohydrate modifier in Modilac is high in dextrins, low in reducing sugars ... provides "spaced" CHO assimilation.

Corn oil replaces butterfat, helps to maintain linoleic acid blood serum levels comparable to those of breast fed infants ... assures optimal caloric efficiency.2 Added vitamins A, C, D, B6 and thiamine appropriately supplement the natural vitamin content.

GERBER BABY FOODS MICHIGAN



1. Mosovich, Luís L., Pessin, Vivian and Lowe, Charles U.; Effects of Milk Composition on Baby Composition, AM. J. Dis. Child. 100: 791-792, 1960.

Gerber,

2. Adam, Doris J. D., Hansen, Arild E. and Wiese, Hilda F.; Essential Fatty Acids in Infant Nutrition, J. Nutrition 66: 555-564, 1958.



Rx the anorexic with no reported contraindications

TENUATE suppresses appetite with no effect on heart rate, blood pressure, pulse or respiration, no alteration of BMR.²

In a recent study of 105 patients who used diethylpropion (TENUATE) throughout their pregnancies,³ the following effects on weight were recorded:

DOSAGE: One 25 mg. Tablet one hour before meals, or 1 new TENUATE DOSPAN Tablet (75 mg.) daily, in midmorning, swallowed whole. An additional 25 mg. Tablet may be taken in midevening to control nighttime hunger.

SUPPLIED: TENUATE Tablets (25 mg. each), bottles of 100 and 1000; TENUATE DOSPAN Tablets (75 mg. each), bottles of 100.

REFERENCES: 1. Alfaro, R. D.; Gracanin, V., and Schlueter, E.: J. Lancet, In press. 2. Huels, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Nulsen, R. O.: Cur. Therap. Res. 2:102, 1960. 4. Horwitz, S.: Personal communication, 1959. 5. Spielman, A. D.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Ravetz, E.: Michigan Acad. Gen. Pract. Symposium, 1959. 7. Decina, L. J.: Exper. Med. & Surg., In press. 8. Scanlan, J. S.: Personal communication, 1959. 9. Kroetz and Storck: Personal communication, 1959.

TENUATE

(diethylpropion)

hunger control with less than 1% CNS stimulation^{2,49}



THE WM. S. MERRELL COMPANY Division of Richardson-Merrell Inc. Cincinnati, Ohio • Weston, Ontario

TENUATE DOSPAN

10-12 HOUR HUNGER CONTROL WITH 1 TABLET

TRADEMARKS: TENUATES, DOSPANS (MERRELL'S CONTINUOUS RELEASE DOSAGE FORM)

a nausea-free pregnancy is every woman's right

BONADOXIN

is right for every woman

stops morning sickness in 94%



Bonadoxin stops morning sickness often with just 1 tablet at bedtime.

Bonadoxin stops morning sickness and treats a possible specific cause—pyridoxine deficiency.

Bonadoxin stops morning sickness without the unpredictability of timed-release formulations.

Bonadoxin stops morning sickness without phenothiazine risks.

EACH TINY BONADOXIN TABLET CONTAINS: Meclizine HCl (25 mg.) for antinauseant action, Pyridoxine HCl (50 mg.) for metabolic replacement. USUAL DOSE: One tablet at bedtime; severe cases may require another tablet on arising. SUPPLY: Bottles of 25 and 100 tablets. Bonadoxin also effectively relieves nausea and vomiting associated with radiation sickness, Meniere's syndrome, labyrinthitis, and motion sickness. Also useful in postoperative nausea and vomiting. Bibliography on request. For infant colic, try Bonadoxin Drops. Each cc. contains: Meclizine 8.33 mg./Pyridoxine 16.67 mg.

and...when your OB patient needs the best in prenatal vitamin-mineral supplementation...OBRON®



New York 17, N. Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being™



THE HEMATINIC WITH BUILT-IN NUTRITIONAL SUPPORT...











Women of menstrual age, many growing children, blood donors, geriatric patients and convalescents may need a hematinic . . . and all can benefit from Livitamin.

Livitamin offers the ideal formula to restore depleted iron reserves and give nutritional support—an important aspect of iron deficiency.

Iron in Livitamin is well absorbed and stored and well tolerated. B complex and other ingredients provide integrated nutritional support.



And Livitamin is a boon for your taste-fussy patients who *should* but *will not* take a hematinic.

LIVITAMIN

... the hematinic with built-in nutritional support

FORMULA: Each fluidounce contains:

Iron peptonized				420 mg.
Manganese citrate, soluble, N.F.				158 mg.
Thiamine hydrochloride		0	۰	10 mg.
Riboflavin				10 mg.
Cobalamin				20 mcg.
Nicotinamide				50 mg.
Pyridoxine hydrochloride				1 mg.

Pantothenic acid.							5 mg.
Liver fraction 1							
Rice bran extract							
Inositol							30 mg.
Choline							

SUPPLIED: Liquid or capsule; also available as capsules, LIVITAMIN with Intrinsic Factor.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

Upjohn

objective:

full term

fetus

complication:

threatened abortion

indicated:

rovera

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Medroxyprogesterone acetate, Upjohn. In scored tablets 2.5 mg. and 10 mg.

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Sterile micronized medroxyprogesterone acetate (17-alpha-hydroxy-6-alpha-methyl-progesterone acetate). 50 mg. per cc. In 1 cc. and 5 cc. size vials. For premenstrual tension Provera plus diuretic plus tranquilizer adds up to logical therapy. Each Cytran® tablet contains 2.5 mg. Provera, 3 5 mg. Cardrase® (ethoxzolamide), and 300 mg. Levanil® (ectylurea).

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DELALUTIN offers these advantages over other progestational agents

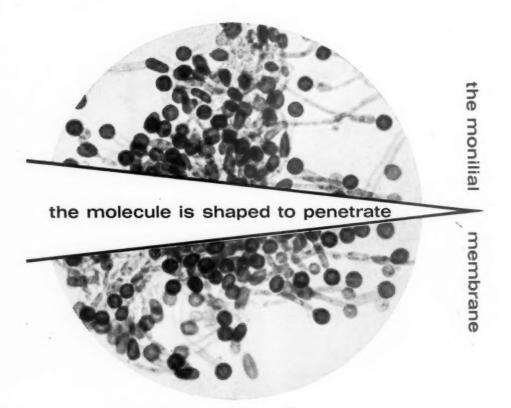
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Lapan, B.: Am. J. Obst. & Gynec. 78:1320, 1959.



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1. Crawford, O. B.: Anesthesiology 14:278, 1953. 2. Wiedling, S.: Xylocaine, The Pharmacological Basis For its Clinical Use, Stockholm, Almquist and Wiknell, 1959.



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neral practitioner, the internist, and the nalike are frequently called on to relieve perform minor surgical procedures that e successfully managed with the aid of irsatile anesthetic. Consistently effective esia may be expected from Xylocaine ve blobecate of its fast and profound action and performe ing ability. It is virtually nonirritating and its its tes and is relatively nonsensitizing, and its size as a wide margin of safety. For topical dirementations with cotton swabs, or by packs, as well as by ged in astillation into a cavity and by application analysis not a surface. Local anesthesia of nerves, plex-30 cc. ses or terminal nerve endings requires indi-



of up didualized volumes and concentrations. For most heavener I use Xylocaine is recommended in consistence of the instance of 0.5%, 1% and 2%, with the metance of successions of 0.5%, 1% and 2%, with the metance of successions of 4% Xylocaine may be used edictable opicing by in those cases where lower concentrations are ineffective or inadequate. The 4% the lower olution may also be used transtracheally and ty ocan for reproduction.

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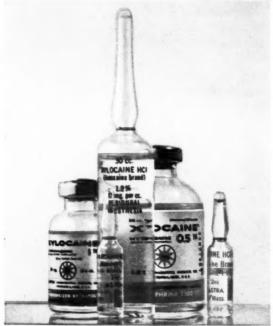
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\$Bryce-Smith, R.: Local analgesic drugs, Brit. M.J. 1:1039 (April 2) 1960.

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ADMINISTRATION AND DOSAGE: For control of nausea and vomiting of pregnancy, a daily dose of 25 to 50 mg. is usually effective. For dosage schedules in other indications, see package insert.

SIDE EFFECTS: Not a phenothiazine, the side effects reported in association with BONINE have been mild and/or transient and consist of occasional drowsiness, dryness of the mouth, and blurred vision. Drowsiness is seen less frequently with BONINE in therapeutic dosages than with most other effective antiemetics.

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More detailed professional information available on request.

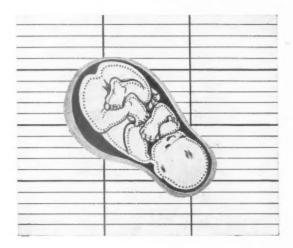


now in threatened premature delivery

Dactil-OB

Brand of piperidolate hydrochloride, hesperidin complex and vitamin C

prolongs gestation / increases fetal survival rate



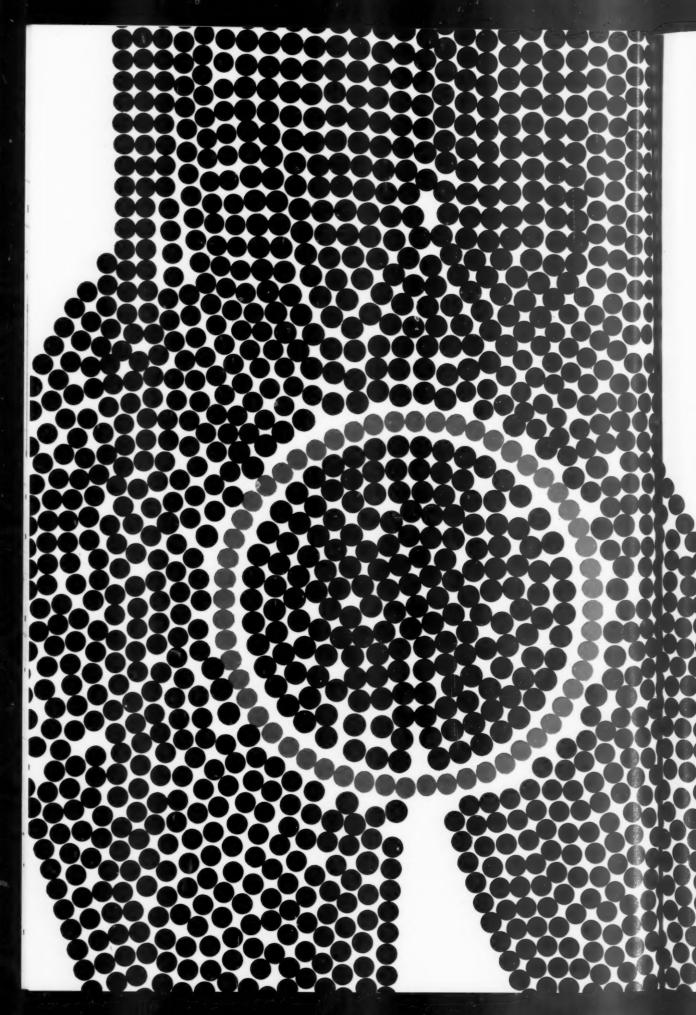
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Dosage: 1 tablet q.i.d. from the beginning of pregnancy in any patient with a history of previous difficulty. For more information send for Dactil-OB brochure.

*Stephens, L. J.; The Prevention of Premature Delivery, presented at the Pacific Coast Fertility Society, Las Yegas, Nevada, November 15, 1959.





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REFERENCES: 1. N. MULLA AND J. J. McDONOUGH, ANN. NEW YORK ACAD. SC., 82:(ART. 1), 182, 1959. 2. L. E. SAVEL, D. B. GERSHENFELD, J. FINKEL AND P. DRUCKER, 181D., P. 186.

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January, 1961

Page 67

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References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.



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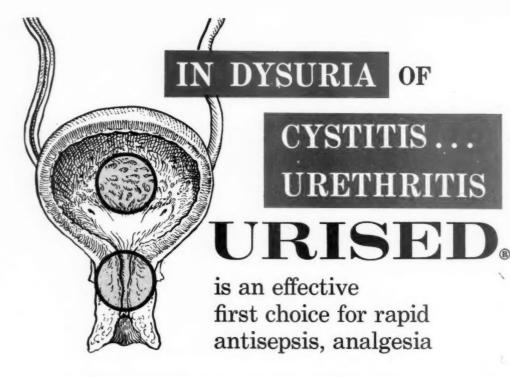
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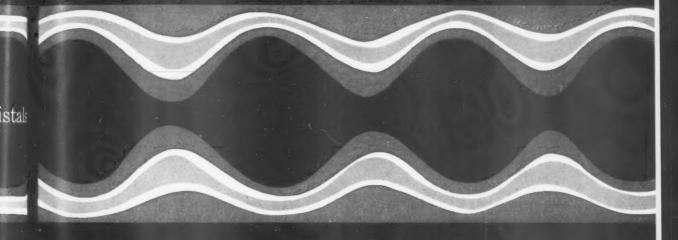
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American Journal of Obstetrics and Gynecology

OBSTETRICS

The carbon dioxide tension of the amniotic fluid

SVEN SJÖSTEDT, M.D. GÖSTA ROOTH, M.D. FRANCO CALIGARA, PH.D. Lund, Sweden

IN RECENT years there has been increased attention directed toward morbidity and mortality in the fetus and the newborn infant. The development of new therapeutic approaches is hampered by our limited knowledge of the intrauterine conditions of the fetus. One way of studying these conditions is to investigate the amniotic fluid.

In our studies^{7, 8} on the oxygen tension (pO₂) of the amniotic fluid we presented proofs that the amniotic pO₂ is equal to or at least closely approaches the tissue tension of the fetus. Similarly the carbon dioxide

tension (pCO_2) of the amniotic fluid and the cutaneous tissues of the fetus will be the same. No measurements of the amniotic fluid pCO_2 seem to have been published.

Material

The amniotic fluid from 50 patients has been analyzed. In 27 cases the amniotic fluid was taken at or near term (late pregnancies) and in 23 cases the fluid was taken from women undergoing legal abortion (early pregnancies). The fluid was obtained from punctures as described in our work on the pO_2 of the amniotic fluid.^{7, 8} No complications were observed during the punctures.

Methods of measuring carbon dioxide tension

The pCO₂ has been calculated from measurements of pH in the amniotic fluid. pH was measured with a Radiometer pH Meter 22 with external meter type PHA 621,

From the Departments of Obstetrics and Gynaecology and Internal Medicine, University Hospital, Lund, and the Wenner-Gren Cardiovascular Research Laboratory, Norrtull Hospital, Stockholm, Sweden.

This study has been supported by grants from the Association for the Aid of Crippled Children, New York, and the Swedish Medical Research Council, Uppsala, Sweden.

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and the pCO2 was calculated with the Astrup1 method. The basis for this is that, if the actual pH is measured first, the pCO₂ may be calculated, once the pH is analyzed, after equilibrations with two gases of known pCO₂. Astrup showed that by plotting the pH from one and the same plasma against log pCO₂ a straight line is obtained. From this line the actual pCO₂ is read off. As this correlation depends upon the Henderson-Hasselbalch equation, it is also valid for other fluids as well as plasma, and preliminary analyses showed that it was valid for the amniotic fluid. The accuracy of the method is said by Astrup to be about ± 1 mm. Hg, which also agrees with our findings.

Results

Fig. 1 gives the pH values from the amniotic fluid. The pH is plotted against gestation time. In the material there are no week to week differences either in the group of early or in the group of late pregnancies. However, as is already apparent from the figure, there is a difference in the pH between the two groups. The mean value early in pregnancy is 7.12 and late in pregnancy 7.04. The difference 0.08 is statistically highly significant (p < 0.001) (Table I).

Table I. Carbon dioxide tension and pH in amniotic fluid

	Early preg- nancies (11-22 weeks)	Late preg- nancies (37-44 weeks)	Difference
Number	23	27	
Mean pCO ₂ (mm. Hg)	50.9	57.3	6.4 (p < 0.01)
Mean pH	7.12	7.04	0.08 (p < 0.001)

The pCO₂ values from the amniotic fluid are shown in Fig. 2. Here again there are no weekly differences but there is a significant difference between the early and late pregnancies (Table I). The mean value early in pregnancy is 50.9 mm. Hg and late in pregnancy 57.3 mm. Hg. The difference is 6.4 mm. Hg (t=3.49; at t=3.51 p < 0.001).

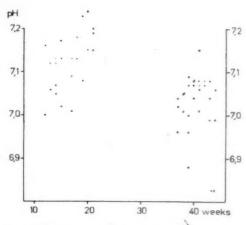


Fig. 1. pH in the amniotic fluid in different gestation weeks.

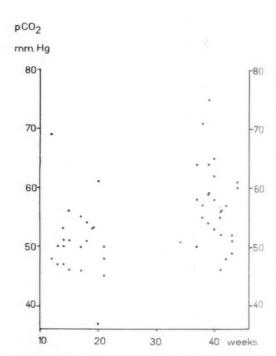


Fig. 2. The carbon dioxide tension in the amniotic fluid in different gestation weeks.

Comment

Haselhorst and Stromberger³ were the first to measure pCO₂ in the umbilical arteries in the infant, and in 4 cases they found values between 45 and 53 mm. Hg. Eastman, Geiring, and DeLawder² gave values between 40 and 65 mm. Hg. James and associates⁴ found a mean of 55 mm. Hg and Wulf⁹ 49 mm. In

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ind In nur laboratory⁶ the mean in 42 cases is 49.4 nm. Hg in the umbilical arteries. This may be compared with the amniotic fluid pCO₂ = tissue pCO₂ where our mean value in late pregnancy is 57 mm. Hg. The difference between the umbilical arteries and the tissues, i.e., 8 mm. Hg, is of the magnitude expected.

The difference in pCO₂ between the group of early pregnancies and the group of late pregnancies is interesting and agrees with the changes in pH and pCO₂ in the umbilical blood of the fetal lamb observed by Kaiser and Cummings.5 The validity of this difference is substantiated by the fact that there is also a difference in pO2 between the same groups. The mean pO₂ in the early pregnancies is 11.0 mm. Hg and in the late pregnancies 7.0 mm. Hg. The difference, 4.0 mm. Hg, is statistically significant (p < 0.01). On the basis of our present knowledge it is not possible to give a satisfactory explanation for this difference. Factors of importance are the size of the fetus, the metabolism of the fetus, and influence from the surrounding gas pressures. For the moment, therefore, this difference should be regarded as a physiological statment and not as a basis for clinical conclusions.

The measurements of pCO₂ in the amniotic fluid are an indication of the intrauterine oxygenation of the fetus. If the tissues of the fetus suffer from hypoxia because of deficient oxygen transportation from the mother across the placenta or because of reduced circulation in the infant, the carbon dioxide will accumulate. If the fetus suffers from chronic lack of oxygen, the increased amount of carbon dioxide should diffuse into the amniotic fluid and give higher pCO₂ figures. The condition may be directly compared with a respiratory acidosis of the adult where there is a hypoxia and a hypercapnia.

Summary

The mean pCO₂ of the amniotic fluid in 23 cases of induced abortion (11 to 22 weeks) was found to be 50.9 mm. Hg. In 27 cases near or at term the pCO₂ was found to be 57.3 mm. Hg.

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Acid-base balance of the amniotic fluid

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THE carbon dioxide tension (pCO₂) in the amniotic fluid is very similar to that in the fetus.1 When there is an increase in the amniotic pCO2 the fetus has difficulty in eliminating CO₂ and in obtaining O₂. Analyses of the pCO2 of the amniotic fluid may therefore prove to be a valuable tool for diagnosis of intrauterine hypoxia and/or hypercapnia. It is convenient to measure the pH simultaneously with the pCO2 analyses, and it is necessary to understand the relationship between these two measurements. It is the aim of the present study to show that a proper interpretation of the acid-base balance of the amniotic fluid may give important information about the fetus.

Methods

All the measurements have been made according to the Astrup² technique as described earlier by us.¹ The principle is that pH is measured first anaerobically and then again after equilibration of the amniotic fluid with two gases, the pCO₂ of which is known. On the basis of these measurements the pCO₂, standard bicarbonate, and bicarbonate content have been calculated from a log pCO₂/pH diagram.²⁻⁴

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This study has been supported by grants from the Association for the Aid of Crippled Children, New York, and the Swedish Medical Research Council, Uppsala, Sweden.

Nomenclature

Studies of acid-base balance have been done almost exclusively on blood, and if changes in pH are due to changes in pCO2 they are called respiratory, as the pCO₂ is regulated by the lung function. By analogy, if changes in pH of the amniotic fluid are due to pCO₂ they are herein called "respiratory type." If the changes are independent of pCO2 they are called "metabolic type." The best measurement for the latter is the standard bicarbonate introduced by Astrup.² In the case of the amniotic fluid the standard bircarbonate is the amount of bicarbonate in milliequivalents per liter present in the fluid after equilibration with 40 mm. Hg pCO₂. It is evident that as the pCO₂ always is 40 mm. Hg when the standard bicarbonate is measured, whatever changes there are in it must be due to nonpCO₂, i.e., metabolic influences.

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Results

Table I shows the tabulated values for 17 cases of early pregnancies, i.e., patients between the twelfth and twentieth weeks of gestation when therapeutic abortion was performed. Table II gives the same values for late pregnancies, i.e., between the thirty-eighth and forty-fourth weeks.

If the early and late pregnancies are compared, it will be seen that pH is lower and pCO₂ is higher in the late pregnancies, as already described. The standard bicarbonate is lower in the late pregnancies, but the difference is not statistically significant (Table III).

In order to establish the importance of

this difference in the standard bicarbonate, the 10 cases with highest and lowest pH have been grouped together. The statistical difference between the means in this group and in the early and late pregnancies is shown in Table III.

As expected, the difference in pCO₂ is much greater between the highest and lowest pH groups than between early and late pregnancies, but the difference in standard bicarbonate also becomes highly significant (p < 0.001).

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The acid-base balance of any fluid depends upon the capacities of its buffer system. The two major buffer systems in blood are the bicarbonate and the protein systems. The latter, amounting to only some 0.3 per cent in the amniotic fluid, will in this case be of minor importance.

In a bicarbonate solution the relation between the pH and pCO₂ is given by the Henderson-Hasselbalch equation. In the Astrup diagram (Fig. 1) this is represented by the line B-O and by any line parallel to this. The position of the line depends upon the amount of bicarbonate present, while the slope indicates the buffer capacity in respect to CO₂. If other buffer systems are present, the line will be closer to the vertical, which means that changes in pCO₂ will not alter the pH so much. This is directly evident from the diagram. Now A-O represents the plasma line. The difference in slope is due to the buffering action of the plasma proteins. The actual line for the amniotic fluid varies in slope between the limits -1.0 and -1.2.

The bicarbonate content of the amniotic fluid is about 15.5 mEq. per liter (range 12.0 to 21.5). This is almost the same value as found by Hanon,⁵ his mean being 16.6 mEq. per liter.

We have given figures for the bicarbonate content of the amniotic fluid because they are already available in the literature and because this is a value-with which every laboratory is familiar. However, it should be remembered that the figure for the bicar-

Table I. pH, carbon dioxide tension, standard bicarbonate, and bicarbonate content of amniotic fluid in early pregnancies

Case	pН	pCO ₂ (mm. Hg)	Standard bicar- bonate (mEq./L.)	Bicar- bonate content (mEq./L.)
1	7.00	69	14.4	15.8
2	7.01	55	13.0	13.1
3	7.02	56	12.4	12.5
4	7.05	53	13.9	14.0
5	7.07	51	15.3	15.0
6	7.08	53	14.3	14.8
7	7.09	46	12.9	13.2
8	7.12	. 50	16.0	16.4
9	7.13	47	15.0	15.4
10	7.13	46	14.4	14.9
11	7.13	54	16.8	17.2
12	7.15	50	16.7	16.7
13	7.16	48	16.6	16.9
14	7.19	45	16.5	16.5
15	7.20	48	18.0	18.1
16	7.23	53	21.2	21.5
17	7.24	37	15.8	16.6

Table II. pH, carbon dioxide tension, standard bicarbonate, and bicarbonate content of amniotic fluid in late pregnancies

Case	pН	pCO ₂ (mm. Hg)	Standard bicar- bonate (mEq./L.)	Bicar- bonate content (mEq./L.)
18	6.88	64	10.9	11.2
19	6.96	58	12.4	12.5
20	6.96	76	15.7	16.7
21	6.99	61	14.2	14.4
22	6.99	51	11.9	12.0
23	7.00	59	14.1	14.2
24	7.01	55	13.0	13.4
25	7.01	55	12.8	13.0
26	7.02	64	15.3	16.4
27	7.04	62	15.9	16.0
28	7.04	49	12.7	12.8
29	7.04	50	12.4	12.8
30	7.05	71	18.4	19.2
31	7.05	57	14.9	15.4
32	7.06	60	16.1	16.8
33	7.06	56	15.0	15.3
34	7.07	65	17.4	18.6
35	7.07	52	14.6	14.6
36	7.07	54	14.3	15.2
37	7.07	57	15.5	16.4
38	7.08	53	15.1	15.2
39	7.08	56	16.3	16.6
40	7.08	58	16.1	16.6
41	7.08	52	14.6	14.5
42	7.09	59	16.2	17.1
43	7.15	45	14.4	14.5

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Table III. Testing the difference between carbon dioxide tension and standard bicarbonate in different groups

	Mean late pregnancies	Mean early pregnancies	Difference	t		p
pCO ₂ (mm. Hg)	57.6	50.5	7.1	3.40	<	0.01
Standard bicarbonate (mEq./L.)	14.6	15.5	0.9	1.44	>	0.05
	Mean 10 lowest pH	Mean 10 highest pH				
pCO ₂ (mm. Hg)	60.2	47.2	13.0	4.66	<	0.001
Standard bicarbonate (mEq./L.)	13.6	16.7	3.1	4.28	<	0.001

bonate does not indicate whether disturbances are of metabolic type or due to changes in pCO₂ or to a combination of the two. These facts are revealed only by knowing the relevant pCO₂ measurement as well as that of standard bicarbonate (or some equivalent figure).

As the pCO₂ is higher and the pH is lower in the late pregnancies than in the early pregnancies it may be justifiable to say that there is a respiratory type of acidosis in the amniotic fluid in the late pregnancies as compared with the early ones. However, it must be remembered that as far as we know this is only a relative acidosis and the term has no pathological significance.

The higher pCO₂ in the late pregnancies is not due to increased pCO₂ of the mothers; Boutourline-Young and Boutourline-Young⁶ have shown that the alveolar pCO2 (which is the same as the arterial pCO₂) of pregnant women decreases by about 3 mm. Hg from the time of early pregnancy to late pregnancy. This drop in the maternal pCO₂ would be expected to give a drop in the amniotic fluid pCO2 too. Since the opposite occurs, it must be because the fetus meets with some difficulty in eliminating CO2, the mechanism of which is not clear, and it may be permissible to regard low pCO₂ of the mother as a compensation in order to facilitate the CO₂ transfer from the fetus.

The standard bicarbonate of the amniotic fluid is about 15 mEq. per liter. In the blood of normal subjects the corresponding value is, according to Astrup, 23 mEq. per liter.

It may therefore be said that compared with ordinary blood the amniotic fluid has a metabolic type of acidosis. This comparison is made only because we are used to acidbase balance figures from the blood. It is somewhat better to compare the standard bicarbonate of the amniotic fluid with that of fetal blood. In 31 cases we have found a mean of 16.8 mEq. per liter in the umbilical arteries. This value may then be compared with that of late pregnancies where the standard bicarbonate is 14.6 mEq. per liter. It follows that there is a slightly higher concentration of fixed acids in the amniotic fluid than in the umbilical arteries of the fetus.

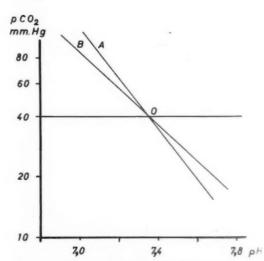


Fig. 1. The pCO₂/pH diagram shows the higher buffer capacity for pCO₂ of the blood plasma (line A-O) compared with a bicarbonate solution (line B-O). (Modified from Siggaard Andersen, O., and Engel, K.: Scandinav. J. Clin. & Lain Invest. 12: 177, 1960.)

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The standard bicarbonate varies between 10.9 and 21.2 mEq., the mean value in the early pregnancies being 15.5 and in the late pregnancies 14.6 mEq. In the two groups with lowest and highest pH values (Table III), this difference in standard bicarbonate is more pronounced and is statistically highly significant. We find that when pH is low this is due to a high pCO2 (mean value 60.2 mm. Hg) and a low standard bicarbonate (mean value 13.6 mEq.). Again, when pH is high the pCO₂ is low (mean value 47.2 mm. Hg) and the standard bicarbonate is high (mean value 16.7 mEq.). This shows that at low pH there are more acid metabolites in the amniotic fluid (lower standard bicarbonate). It may therefore be stated that when the amniotic fluid has a decrease in pH due to retention of CO2 there is at the same time a decrease in pH due to acid metabolites; in other words, when there is a respiratory type of acidosis there is in addition a metabolic type of

This is the opposite of what happens in blood. If a person has a respiratory insufficiency and therefore retains CO₂, initially there will be no changes in the standard bicarbonate, but after a while a metabolic compensation will be made by the kidneys, the urine will contain increasing amounts of acid and the standard bicarbonate in the blood will be increased.

The amniotic fluid is in contact with the fetus and some quantity is inspired and expired by the fetus. More important, however, in this respect is the fact that the fetus urinates directly into the amniotic fluid. If the fetal kidneys have the same pH regulation mechanism as the ordinary kidney, we would expect increased excretion of acid when the pCO₂ increases, and this is what has been found. The present results therefore indicate that the fetal kidney has a pH regulative mechanism. Most cases of low standard bicarbonate are found in the late pregnancies, but some are found in the group of early pregnancies and the lowest value in this group, 12.6 mEq. per liter, is found in a fetus aborted in the fifteenth week. It

therefore seems that the pH regulation by the kidneys starts at a relatively early fetal stage.

Weisbrot and associates,⁸ studying cord blood, showed that in some cases of asphyxia there is both a respiratory and a metabolic acidosis. In these cases, too, the kidneys will try to compensate by eliminating acid in the urine, and the amniotic fluid would also have a metabolic as well as a respiratory type of acidosis.

Summary

1. The pH of the amniotic fluid is lower than that of the blood because of a relatively high pCO₂ (respiratory type of acidosis) and relatively large amounts of fixed acids as shown in a low standard bicarbonate (metabolic type of acidosis) and because its buffering action is less than that of blood (low protein content).

2. When there is increased pCO₂ in the amniotic fluid there is at the same time a metabolic type of acidosis.

3. This metabolic type of acidosis is probably due to an excretion of acid in the urine by the fetus as a compensation for a respiratory or metabolic acidosis of the fetal blood.

4. The measurement of pCO₂ and standard bicarbonate of the amniotic fluid offers an easy way of estimating the gas exchange of the fetus in utero.

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Clinical study of hypertensive disease in pregnancy

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IN PRESENTING a clinical study of 224 cases of hypertensive disease in pregnancy, one must admit the great difficulty in the proper classification of these patients. Approximately 1,000 records were reviewed. Many cases were discarded as borderline with diagnosis not established. Others were not used because of lack of factual data. Some were unclassified as they were seen only at the time of delivery. Lack of proper followup made others fall in the unclassified group. Even a few of this series were subject to debate between the authors. However, it is believed that the cases presented represent an accurate diagnosis. Table I represents the classification of our cases.

Our definition of essential hypertension is a prepregnant blood pressure of 140 systolic and 80 diastolic or higher or the presence of this level in the first half of pregnancy. The urine examination must be negative. This level of blood pressure must be present 3 months or more post partum.

If, in addition to the existing hypertension, there should be a rise in blood pressure and the appearance of albumin in the latter part of pregnancy, this is assumed to be a superimposed pre-eclamptic toxemia.

The patient with severe or advanced hypertensive disease with secondary renal involvement is classified under renal disease as it is this disease that is important, not the hypertension.

Under the diagnosis of renal disease, we include those patients in whom the diagnosis has been definitely established in the nonpregnant state. However, many patients with renal disease do not give a history of previous kidney trouble. The presence of albumin and casts in the first half of pregnancy, with or without hypertension, is assumed to indicate renal involvement. This must be present 3 or more months post partum. Failing ability of the kidney to concentrate is an early and helpful sign of renal disease. A maximum concentration of 1.1012 confirms the diagnosis. Renal function tests have proved of little value as they remain within normal limits until the disease is quite evident. Actually, the progress of the pregnancy confirms the diagnosis in most cases.

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The diagnosis of superimposed toxemia is difficult to make in the presence of renal disease. Only 3 of our cases appeared to fit in this category. However, a sudden rise in blood pressure with an increase in albuminuria and no sign of nitrogen retention suggests this possibility. Whether this is true toxemia or not, it is a poor prognostic sign and usually indicates the termination of the pregnancy.

A normal blood pressure and urine during the first half of pregnancy followed by a rise of blood pressure and the development of albuminuria in the last trimester is our criteria for the diagnosis of pre-eclamptic toxemia. In the great majority of patients, this is preceded by excessive weight gain (fluid retention). To confirm the diagnosis, the symp-

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oms must disappear within 2 weeks after delivery. There should be no residual hypertension or albuminuria at 3 months post parium. In pre-eclampsia, we believe that there no definite hypertensive level that is of diagnostic value. It is the rise over pre-existing levels, particularly diastolic, that is important. An increase in pressure of 20 to 30 mm. Hg and the development of proteinuria indicates pre-eclamptic toxemia no matter what the actual level of the blood pressure. Also, the severity of the disease is not always dependent on the actual level of the hypertension. The amount of albumin in the urine appears to be a better prognostic sign. The development of cerebral signs, headache and disturbance of vision, is always evidence of severe disease no matter what the other signs may show.

Essential hypertension

Essential hypertension is the most common hypertensive state observed in pregnancy in this clinic. Uncomplicated by pre-eclamptic toxemia, we have found it to be a rather benign complication of parturition. The incidence in Negro patients is approximately three times that in white. It has been our observation that the obstetrician sees this condition in its earliest stages.

In the series presented, 85 per cent of the patients with essential hypertension progressed to delivery of a full-term normal infant. As this clinic has an over-all incidence of 14 per cent premature deliveries, the patient with essential hypertension does not differ from the normal group. There was no case in which induction of labor was per-

fer from the normal group. There was no case in which induction of labor was performed for this complication. Of the 3 still-births in this group, two were the result of premature separation of the placenta. This supports our belief that fetal death in utero need not be feared as the result of this condition. The third intrauterine death appeared in a patient who had been on antihypertensive drugs for 6 weeks. The blood pressure had fallen 50 points and remained at that level. At 36 weeks the baby died in utero. Our only explanation was that fetal anoxia

resulted from the lowering of the hyperten-

sion. While this is impossible to prove, we do feel that this possibility must be considered when antihypertensive drugs are used.

There was a cesarean section incidence of 4 per cent in this series. This is the same as the general incidence. The cesarean sections performed were for general obstetrical indications unrelated to the hypertension.

Thirteen cases in this group were in young primiparas. With one exception, the hypertension had not been noted previous to the pregnancy. As this is an asymptomatic condition, the obstetrician is usually the first medical contact with these young women. Therefore, we tend to see this complication earlier than our medical associates. Certainly this disease can develop at an early age.

From our experience with essential hypertension in pregnancy, we have come to believe that this in itself is a rather benign complication. The hypertension is not responsible for any severe trouble for either mother or baby. It is of interest that even with good prenatal care that 2 patients with twin pregnancies developed pre-eclamptic toxemia. As these were the only twins in this group, this does indicate that twins may present a hazard to these patients.

Essential hypertension with superimposed toxemia

In addition to the 74 patients with essential hypertension, there were 16 patients with superimposed toxemia. Of these, 15 were unregistered patients who presented with this condition. A previous history of hypertension was known in some. Others demonstrated a permanent hypertension in the postpartum follow-up. The presence on admission of hypertension, proteinuria, and excessive weight gain gave evidence of pre-eclamptic toxemia.

While this is a small group, it does confirm our clinical impression that the combination of these two syndromes causes a more acute disease than pre-eclampsia alone. There were 3 premature separations of the placenta with 3 stillbirths. Less than half these patients had a normal full-term infant. Including the 3 premature separations, there were 9 prema-

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ture births. Three of these were spontaneous and 6 induced. The total of 5 stillbirths presents a poor fetal salvage. No cesarean sections were performed as vaginal delivery was successful in all cases. There were no cases of eclampsia because the patients presented themselves in time for delivery before convulsions developed.

Certain patients with essential hypertension will develop urinary tract infection and proteinuria. This can easily lead to a mistaken diagnosis of pre-eclampsia. Such cases can be easily relieved by treatment of the urinary tract infection and allowed to progress safely to term.

From the study of our 79 cases of preeclamptic toxemia, certain conclusions may be drawn: Pre-eclamptic toxemia is not a primary cause of spontaneous premature labor. There were no such labors in our series. In addition, toxemia is not a cause of intrauterine death except secondary to premature separation of the placenta. The stillbirths in our group were all in cases of abruptio placenta. However, since in about one third of our cases labor was induced or delivery was by cesarean section in the premature state, there is a considerable fetal loss in the neonatal period.

Approximately two thirds of our cases of pre-eclamptic toxemia appeared in primiparas. Of interest is that the elderly primipara appeared as susceptible to this disease as her younger counterpart. It is certainly true that pre-eclampsia appears more frequently in the multipara with an underlying hypertension but it does occur with no chronic vascular or renal pathology. The majority of multiparas with hypertension and proteinuria in later pregnancy will show underlying pathology if followed carefully after delivery.

Premature separation of the normally implanted placenta appeared in 10 per cent of our cases. The appearance of this complication is entirely unpredictable. While most patients arrived in the hospital with separation already evident, in 2 the separation occurred while they were under medical care on our wards. The risk of this complication must al-

ways be kept in mind in the prolonged medical treatment of pre-eclamptic toxemia.

The rare but serious problem of afibrinogenemia has appeared twice in thi group. In 2 patients this was controlled with adequate amounts of fibrogen, although 1 patient required 13 Gm. All our patients with premature separation of the placenta who have been tested for the blood fibrogen level have shown a definite fall. While only 2 cases fell below the critical level of 100 mg., many others showed levels below 200 mg. Therefore, afibrinogenemia appeared in relative degree in most of the cases of premature separation of the placenta, although causing a clinical problem in only a few. This is of importance in that the time interval between separation and delivery may be an important factor in the development of this serious situation.

Approximately 20 per cent of our patients with pre-eclampsia were delivered by cesar-ean section. This was due to the fact that these cases were primiparas with severe disease developing several weeks before term. They were not responding to treatment and their conditions were not favorable for induction.

It has been our custom to treat the patient who arrives in the hospital with a severe toxemia medically for 12 to 24 hours before attempting delivery. The treatment consists of heavy sedation, mercurial diuretics, and large doses of magnesium sulfate. Most patients respond favorably to this treatment with marked diuresis, a fall in blood pressure, and a decrease in proteinuria. There is also a decrease in the hyperactivity of the reflexes. Following such treatment, these patients appear to undergo cesarean section or vaginal delivery in a more favorable manner. There also appears to be less danger of postpartum eclampsia.

The use of magnesium sulfate has been routine in our clinic for many years. This drug is used entirely as an anticonvulsant and has proved eminently satisfactory. It can be given in large doses over a period of 48 to 72 hours. An original dose of 10 Graintramuscularly can be followed every

hours by 5 Gm. of this drug. A careful observation of the knee jerks will give ample warning of magnesium intoxication. However, this has not happened in our experience.

In the situation of a mild pre-eclampsia which is responding favorably to treatment, the question arises as to the danger of permanent renal or vascular damage resulting from a prolonged course of the disease. None of our patients developed demonstrable renal disease after an episode of toxemia. A certain number of patients will show residual hypertension months or years later. Whether this is a result of the disease or simply the development of a latent hypertension is a much debated point. Certainly many women do develop hypertension after a normal pregnancy. In any case, we do not hesitate to use medical treatment in a patient with mild pre-eclampsia for several weeks in the attempt to salvage a premature baby.

There were 7 cases of eclampsia reported in this series. Four were in postpartum and 3 in antepartum patients. All cases were among unregistered patients. It is of interest that in spite of an incidence of 20 per cent unregistered patients that there were only 7 cases in 5 years. There has been no case of eclampsia during the past year. This is a remarkable change in a clinic that 25 years ago averaged 25 to 30 cases per year. While good prenatal care should eliminate most cases of eclampsia, it is hard to explain the absence of this disease in the unregistered patient. Possibly, the public is better educated and patients report to the hospital with earlier symptoms. Even among patients with no prenatal care, it is rare for a woman to stay at home until convulsions develop. Most come to the hospital in time to be delivered before eclampsia appears.

Postpartum eclampsia is not a great problem in regard to treatment. These 4 patients did well with heavy sedation. Having already been delivered, they were actually on the road to recovery even though they did develop convulsions. Their convulsions appeared soon after delivery, within 12 to 24 hours. We have not seen a true case of eclampsia more than 72 hours after delivery. In each case reported, the patient arrived with a severe and fulminating pre-eclamptic toxemia, were delivered within a few hours, and went into convulsions shortly after the termination of the pregnancy. With heavy sedation, these patients recovered from the eclamptic state within 12 hours. They were delivered by cesarean section before convulsions developed, this markedly improved their prognoses as cesarean section is contraindicated during the eclamptic state.

The 3 patients with antepartum eclampsia had all had convulsions before their admission to the hospital. It is of interest that the first symptom reported by 2 of these patients was that they were watching television and suddenly could not see the picture. On admission, the patients were still having convulsions. They were treated with heavy sedation, morphine, barbiturates, and large doses of magnesium sulfate. An inlying catheter was inserted and the urinary output carefully checked. Urinary excretion is an important factor in the prognosis and treatment. After the initiation of therapy, the convulsions ceased within a few hours.

It is extremely difficult to estimate when a patient who is under heavy sedation is actually out of coma. Any response to speech is a most helpful sign. Observation of the patient's general reactions and movements are of importance. The few hours after recovery from eclampsia are extremely vital as this is the most favorable time for delivery. This is particularly true if cesarean section is to be performed. While cesarean section itself carries a high maternal mortality if performed during the eclamptic state, it has been our procedure of choice and has proved to be a lifesaving measure when the patient has recovered from coma and convulsions. This is particularly true in the young primipara with a premature baby and an unfavorable cervix. The majority of patients with eclampsia will fall in this group.

The 3 patients in this report made an excellent recovery. Two have had additional pregnancies with no complications and no signs of residual damage from the episode

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of eclampsia. Once all signs of the eclampsia had cleared, the patients were discharged from the hospital. With no sign of any residual disease at 3 months post partum, the patients were allowed to proceed with further pregnancies.

Two of the 3 patients with antepartum eclampsia were delivered of stillborn infants. There is a high fetal loss in this condition which cannot be avoided. The mother is in such a critical state that all efforts must be directed toward saving her life and any heroic endeavor to save the infant may end in disaster for both mother and child.

Renal disease

Renal disease in pregnancy is one of the most serious medical complications with which we have to deal. The type of renal disease involved is often difficult to determine. From the clinical point of view, the classification of the type of renal involvement is not of major significance. Such detailed investigation is of interest from a statistical and research angle, but is of no great value in the immediate treatment of the situation. The great majority of our cases of renal disease in pregnancy were diagnosed as chronic pyelonephritis. Half of these patients had bacteriuria or positive urine cultures during pregnancy. Many gave a past history of attacks of acute pyelonephritis, but others had a negative history. Several had had repeated attacks of acute pyelonephritis during previous pregnancies.

The second largest group of renal disease during pregnancy is that secondary to essential hypertension. As stated earlier, we classify these women under renal disease rather than hypertension because the renal condition is the major problem. We have records on patients over a period of 20 to 25 years in whom the course of essential hypertension is most characteristic in its progress into renal complications. Most of these women have had many pregnancies but the number of pregnancies appears to have little effect on the development of renal disease.

In 8 cases in which the records date back 20 or more years, a moderate hypertension was present with the first pregnancy. As the patients were followed through additional pregnancies their pressures showed a slow, steady rise. At around 30 years of age, the hypertension levels were approximately 160/90 mm. Hg.

In the middle thirties, the averages were over 200 systolic and 100 diastolic. At this time, signs of renal impairment appeared with proteinuria and some cases of renal failure and fetal death in utero began to occur. The disease continued to progress and there were 3 fatal cerebrovascular accidents a year or more after the last pregnancy. It certainly is not advisable for the patient to continue to become pregnant during this progressive renal deterioration, but such matters are not always under our control.

Chronic glomerular nephritis is the least common type of renal disease seen in our clinic. There were 3 cases in our series. Such patients usually have a past history of acute glomerular nephritis and the diagnosis has been established previous to pregnancy. The specific diagnosis during pregnancy is difficult and may easily be missed. There were 2 cases of renal disease in diabetic patients.

While the differential diagnosis of renal disease is of interest, it is the amount of kidney reserve that is of paramount importance. For reasons not clearly understood, pregnancy throws a very heavy load on kidney function. It may be the most delicate of all tests for renal function. One sees many patients who show no sign of any kidney trouble in the nonpregnant state and yet do not have sufficient kidney reserve to undergo a normal pregnancy. During a given pregnancy, these patients may show proteinuria and even casts, and yet 3 months post partum have normal urine and normal renal studies. After repeated pregnancies, they will in many cases show signs of renal disease in the nonpregnant state.

There was one case of premature separation of the placenta among our series of renal disease. In contrast to pre-eclamptic toxemia, renal disease does not appear to be a predisposing factor in the development of this complication.

Table I

	Essential hypertension (74)	Essential hypertension with pre-eclampsia (16)	Pre-eclamptic toxemia (79)	Renal disease
Premature separation of				
placenta	2	3	7	1
Full-term delivery	65	7	54	19
Spontaneous premature				
labor	2	3	0	20
Total premature (spon-				
taneous and induced)	5	9	25	36
Stillbirth	3	5	5	7
Superimposed pre-		-		
eclampsia				3
Primipara	13	2	47	8
Cesarean section	4	0	16	16
Eclampsia	0	0	7	0

Spontaneous premature labor appears to be a characteristic termination in chronic renal disease. Approximately one third of our patients went into labor prematurely. In the unregistered patient who enters the hospital in labor and is delivered of a premature baby, alive or stillborn, which is followed by a small fibrotic placenta containing white and yellow infarcts, the diagnosis of renal disease is suggested. Apparently, intrauterine death and premature labor are the result of this poorly developed and infarcted placenta. The type of placenta is most characteristic of renal disease and may be the basic reason for the high fetal loss in this condition.

In another third of our patients either labor was induced prematurely or they were delivered by cesarean section because of failing kidney function. Only one third of these patients were delivered of full-term infants.

There were 7 stillbirths in this group. In 5 cases of stillbirth observed previous to labor, there was a definite arrest in uterine growth for 2 to 3 weeks previous to death in utero. This has been such a marked clinical observation in our experience that such arrest in growth has now become an indication for immediate delivery. In fact, our salvage of full-term infants has been so poor hat our policy at present is to deliver these patients at approximately 36 weeks. Some full-term babies have died during labor and others during the neonatal period.

There were 3 cases that were diagnosed as superimposed pre-eclamptic toxemia. In each case, the patients had been progressing in an unchanged state and then suddenly developed a marked rise in blood pressure and increase in proteinuria. They become critically ill in a matter of hours in contrast to the more gradual change for the worse characteristic of renal disease. Also, there was no sign of nitrogen retention which usually is present in renal failure.

Sixteen patients were delivered by cesarean section. These were cases in which renal failure had developed or was imminent. Time was an important factor. In contrast to the patient with eclampsia, these patients respond well to this type of delivery. The rapidity of their recovery to their nonpregnant state was most gratifying.

Comment

The series of cases presented in this paper is too small to be of any statistical value. They represent only a part of the cases observed by the authors during the 5 year study of this problem. Many cases had to be discarded because of insufficient prenatal or postpartum study. In a large city hospital, many patients are seen in an acute state and never return for further treatment. Because of the difficulty of correct diagnosis, these patients cannot be accurately classified. However, they do add considerably to clinical impressions and experience.

There were no maternal deaths as a result of hypertensive disease in pregnancy during the period of this study. It is true that we know of 3 patients who have died a year or more after their last pregnancy. These were patients with severe hypertension and renal disease whose pregnancies were terminated early with no fetal salvage. There may be others of whom we do not know. Certainly, there were some in whom the prognosis was extremely poor. The fact remains that pregnancy per se was not the precipitating cause of death. We were fortunate that no patient was admitted in extremis, too late for any treatment. There were several that were admitted in renal failure but they responded well to prompt delivery. With proper care and prompt action, when indicated, a maternal death should be a rare event in hypertensive disease in pregnancy. This does not mean that pregnancy is of little danger or that it should be encouraged in the woman with damaged kidneys.

Essential hypertension without kidney disease has proved to be a rather benign complication of pregnancy. The pregnancy appears to have little effect on the progress of the hypertension and the hypertension has no serious effect on the pregnancy. All effort in these cases should be directed to the prevention of a superimposed pre-eclamptic toxemia. Prevention of sodium retention will usually accomplish this purpose. The use of antihypertensive drugs to lower blood pressure is of little value, and in fact may endanger the fetus by diminishing the blood supply to the placental area. Should preeclampsia develop in the patient with essential hypertension, prompt delivery is often indicated as this is apt to be a severe type of toxemia.

With proper supervision of the normal pregnant woman, pre-eclamptic toxemia is largely a preventable disease. Immediate treatment of any sudden or excessive weight gain is the important treatment in the prevention of toxemia. All such gain in weight must be considered to be due to sodium and

water retention. It is extremely dangerous to assume that weight gain is due to deposition of fat. Clinical edema is frequently absent even with the retention of large amounts of fluid so this cannot be used as a criteria of water retention.

Immediate delivery is essential if the preeclamptic toxemia does not respond to treatment. Any cerebral symptoms are a sign of severe toxemia. Increasing proteinuria is a poor prognostic sign no matter, what the level of the blood pressure. Large amounts of albumin in the urine are of more significance than a high blood pressure. Even the patient with mild toxemia should be delivered as soon as the infant is reasonably mature.

Renal disease is a most serious complication of pregnancy. The type of renal disease is less important than the amount of renal damage present. Depending on the amount of kidney reserve, the patient may or may not be able to pass safely through pregnancy. If the patient has an established diagnosis of chronic nephritis in the nonpregnant state, the prognosis is poor with a marked risk of developing renal failure during pregnancy. Such patients must be carefully supervised and pregnancy terminated at the first sign of kidney failure. Increasing proteinuria with casts, sudden gain in weight, and rise in blood pressure are signs of danger. Any sign of nitrogen retention is an indication for termination of pregnancy. If the nonprotein nitrogen level rises above 60 mg. per 100 c.c. whole blood and remains there for one week, the infant must be delivered. Sodium must be severely restricted during the entire pregnancy. At the first sign of any decrease in renal function, the patient must be hospitalized and frequently kept there until delivery.

Because of the danger of intrauterine death during the last 4 weeks of pregnancy, patients with definite renal disease should be delivered at 36 weeks. Even if such infants live until term, there is a high fetal loss during labor and in the neonatal period.

Pregnancy does appear to have an adverse effect on already damaged kidneys. Each

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pregnancy may aggravate the existing renal condition. Patients with mild kidney disease may be allowed to try for one or two children, but should be fully warned of the dangers involved. Patients with severe kidney disease should be advised against becoming pregnant.

Conclusions

- 1. Essential hypertension is not a serious complication of pregnancy.
- 2. Pre-eclamptic toxemia is largely preventable in normal pregnant women and in

those with essential hypertension. Restriction of sodium is the basic prophylaxis.

- 3. Rapid or excessive weight gain must be eliminated to prevent the development of pre-eclamptic toxemia.
- 4. Renal disease is a most serious complication with a poor fetal salvage. Signs of impending renal failure are the indication for immediate delivery.
- 5. Premature labor and/or fetal death in utero is a frequent result of renal disease in pregnancy.

A comparison study of antihypertensive drug therapy and the modified Stroganoff method in the management of severe toxemia of pregnancy

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"TOXEMIA OF PREGNANCY" is a syndrome consisting of proteinuria, edema, hypertension, and, in severe cases, convulsions and/or coma occurring in pregnant women 24 or more weeks gravid or recently delivered. Although unrecognized as such in early recorded medical history it undoubtedly was a very important cause of excessive perinatal and maternal mortality.

According to Dieckmann,¹ early writings of both the Egyptians and Chinese warned of the dangers of convulsions encountered with pregnancy. Hippocrates^{1, 2} also called attention to the fact that headaches, convulsions, and drowsiness were ominous signs when associated with pregnancy. For many years a state of confusion existed with regard to convulsive disorders, and all diseases involving seizures or clonic contractions were considered forms of epilepsy.

Dexter and his associates³ mentioned that the term "eclampsia" first appeared in a treatise on gynecology written by Varandaeus in 1619; clonic spasms in association with pregnancy were first described by Pew in 1694; and in 1772 De la Motte recognized that prompt delivery of pregnant women with convulsions favored their recovery. Since these early days numerous studies have been carried out in an attempt to find the cause of this phenomenon. Obstetrics and gynecology has made considerable progress over the years in the study of related anatomy, physiology, and endocrinology but the true etiology of toxemia of pregnancy still remains an enigma.

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Historical background of management of toxemia

Toxemia of pregnancy has been a therapeutic problem since it was first recognized as a definite disease entity. Its treatment has undergone an evolutionary process consisting of six periods as described by Dieckmann: The first period, beginning in 1745 and lasting approximately 100 years, was considered a nonoperative era and had as its stalwarts purging, sweating, and blood letting. The second period began about 1845 and lasted approximately 50 years. This was characterized by the initial introduction of Veratrum viride as well as the more radical trend toward immediate delivery by manual dilatation of the cervix. Periods three and four overlapped each other, beginning about 1895 and terminating in 1915. They represented the era of ultra radicalism. During this period immediate delivery by cesarean section, vaginal hysterotomy, or accouchement forcé (Bossi dilator) was the treatment

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This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

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of choice for toxemia. The years 1915 to 1927 brought the fifth period into focus with its swing toward conservative medical management utilizing intravenous hypertonic glucose solution, sedation, elimination, and parenteral magnesium sulfate. The sixth and present era began in 1928 and is characterized by a more conservative obstetric management which utilizes the good facets of the previous periods but discards the obviously radical and dangerous measures responsible for poor fetal salvage.

All periods as described were overlapping eras of therapy which came into existence after the discovery of a new drug, procedure, or method of treatment by a noted person of the time. A wide variety of both operative and nonoperative methods was used in an attempt to lower the exceedingly high maternal mortality rates. Some of these, such as the retromammary injection of potassium iodide or air, radical mastectomy, renal decapsulation, trephining of the skull, massive venesection, lumbar puncture with withdrawal of large amounts of spinal fluid, and massive doses of thyroid, undoubtedly seem barbaric. When one also considers the radical procedures of the day for emptying the uterus, however, it becomes quite obvious that the accoucheurs of that period were desperate in their attempts to conquer a disease with a fantastically high mortality rate.

In the year 1900 Stroganoff^{1, 2} first astounded the medical world with his reported lowered incidence of maternal mortality. His uncorrected figure of 5.4 per cent compared quite favorably with the reported 17 to 29 per cent for English and European clinics and the 21 to 49 per cent⁵ for American clinics of that same period. His subsequent report4 in 1926 carried an uncorrected maternal mortality rate of 2.6 per cent and a fetal and neonatal rate of 16.6 per cent which, when corrected for previability (weight less than 2,000 grams) became 6 per cent. Both his original and his improved prophylactic methods6 had as their basis profound sedation and narcosis to prevent and control seizures. A darkened room was essential. Chloroform, chloral hydrate, and morphine were used liberally. Later both rupture of the membranes⁷ and magnesium sulfate8 were incorporated into the management and the administration of oxygen during fits8 was instituted. Stroganoff,4 however, insisted on strict compliance with his methods as outlined if satisfactory results were to be expected. Almost immediately Speidel,9 Stander,10 and others5 began to modify the Stroganoff method with equally satisfactory results. So many modifications of the original method have appeared since that time that, except for the general concept of heavy sedation, the exact mode of treatment must be defined and described for clarification in each case. Some of these modifications are still in existence and represent one aspect of present-day therapy for toxemia.

Magnesium sulfate as a sedative was introduced by Titus and his co-workers1 in the early 1920's. The magnesium ion is known to depress nervous excitability at the neromuscular junction in a manner similar to that of curare.11, 12 It likewise acts as a central nervous system depressant, and some workers8, 13-15 feel that vital medullary centers are particularly vulnerable. The characteristic hyporeflexia produced by this drug is derived from this dual origin and serves as a gross clinical level of its effectiveness. 12, 13, 16 Used in conjunction with either sedation or the newer antihypertensive medications, parenteral magnesium sulfate represents one of the most popular and effective adjuncts of toxemia therapy used today.

Although its original discoverers are not known, Veratrum viride was first introduced between 1850 and 1865.1, 2, 6 Initial work was done with the crude alkaloids and side reactions were common. The small margin of safety between the therapeutic and the emetic dose, changing sensitivity to a given therapeutic dose, and the occurrence of acute vascular collapse with subsequent intrauterine fetal death and an occasional maternal death were very real problems. The dangers of crude Veratrum therapy were emphasized by Schwarz and McNalley.17

This led to abandonment of this form of treatment by almost everyone except Zinke and the Cincinnati¹ group who have continued to use it throughout the years. In recent studies Finnerty, 18-20 Raber, 21 and others, 22-25 using the more purified Veratrum derivatives, reported a marked decrease in side reactions and emphasized the value of this agent in the treatment of toxemia.

The past two decades have been studded with intensive research and clinical investigations and it is now a generally accepted concept that the fundamental pathophysiologic disturbance of toxemia is a generalized arteriolar vasoconstriction with a secondary increase in peripheral vascular resistance. It is known that these phenomena are not limited entirely to the peripheral circulation but likewise involve such vital organs as the kidneys, 13, 26 brain, 16, 27-29 heart, 13, 26 retinas, 30-32 and the pregnant uterus. 16, 33, 34 Despite the general acceptance of this concept, until the last 5 to 10 years the primary methods of management of toxemia consisted of heavy sedation either alone or in combination with parenteral magnesium sulfate and/ or hypertonic glucose solution. As emphasized by Assali¹⁶ and others, 1, 11, 13 the primary pharmacodynamic action of massive sedation, regardless of the agent used, is depression of the central nervous system. This form of therapy, while of some value in depressing cerebral irritability, does little or nothing to reverse the underlying responsible pathophysiologic process of vasoconstriction.

Recent research has uncovered a new group of medications, the primary action of which is vasodilatation. Some of these agents are new synthetic chemical compounds, others are purified preparations of drugs known for many years. The use of these products offers, however, a logical and pharmacophysiologic approach to the problem of toxemia therapy. Sellers¹³ has published an excellent classification of these medications based on their site of action. The adrenergic ganglionic blocking agents have proved to be of only limited value in the treatment

of toxemia^{3, 12, 13, 35, 36} because of both their method of action and their unusual potency.¹¹⁻¹³ On the other hand, drugs with a central blocking action have been found to be very effective in the treatment of toxemia because of their apparent direct effect on the generalized vasospasm and resultant hypertension.^{12, 13, 35, 36}

Bryant and Flemming,^{37, 38} Raber,²¹ Finnerty,^{18, 19} and others^{24, 25, 39} have all reported on the value of *Veratrum viride* and its purified derivatives both alone and in combination with other agents. Assali,^{26, 39-41} McCall,⁴² and Finnerty⁴³ have reported favorably on the action of 1-hydrazinophthalazine (Apresoline) and cryptenamine (Unitensen) and have outlined methods of using these agents in the management of toxemia. The Rauwolfia derivatives have likewise been studied by a number of observers^{44, 45} and have been found to yield favorable results.

Because antihypertensive medications attack the basic pathophysiologic disturbance in toxemia, it seems logical that this approach would give the best over-all results for both the mother and the fetus. It is with this presumption in mind, as well as to compare the results of two distinct and different methods of therapy, that this study was undertaken.

Material

During the 3 year period from July 1, 1953, to June 30, 1956, a total of 13,771 patients were delivered at the U. S. Naval Hospital, San Diego, California. Of this number, 693 cases or 5.03 per cent were coded as showing a variant of toxemia of pregnancy according to the Joint Armed Forces Statistical Classification and Basic Diagnostic Nomenclature of Disease and Injuries—1949. All charts were reviewed and data compiled on special analysis sheets devised for the study.

The Definition and Classification of Toxemias of Pregnancy, as established by the American Committee on Maternal Welfare, April 1, 1952, was strictly adhered to in this study. Cases classified as toxemia purely on 61

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the basis of excessive weight gain without the presence of other diagnostic signs were not included. Those patients manifesting only transient antepartum, intrapartum, or postpartum elevations of blood pressure of less than 6 hours' duration are likewise excluded. Cases of confirmed hypertensive disease in the prepregnancy state were not included unless definite substantiated superimposed toxemia developed.

This particular period from July 1, 1953, to June 30, 1956, was chosen because during this time two different methods of treatment of toxemia were in use. The first and earliest was a modification of the Stroganoff technique which utilized the principle of heavy sedation. Morphine, barbiturates, and chloral hydrate were used liberally alone and in combination with parenteral magnesium sulfate. A darkened, quiet room was maintained and oxygen was administered during periods of potential or actual convulsions. Patients treated by this method are referred to as the "Stroganoff group."

The second and later method of management utilized both oral and intravenous antihypertensive medications and no heavy narcosis. Patients with mild pre-eclampsia with blood pressure readings below 160/110 were treated with bed rest, parenteral magnesium sulfate, and oral antihypertensive medications. In cases of severe pre-eclampsia where the blood pressure was above 160/110 or signs of marked cerebral irritability were present, antihypertensive medication was started via the intravenous route along with parenteral magnesium sulfate. As with the modified Stroganoff method, a darkened and quiet environment was maintained. Oxygen was administered to all patients manifesting signs of extreme irritability and sodium Amytal was used intravenously to control actual convulsions when present. These patients are referred to as the "antihypertensive group."

Review of the 693 cases coded as toxemia or a variant of toxemia yielded 130 acceptable cases for study, for a corrected incidence of 0.94 per cent. Of this group 66 were managed with the modified Stroganoff

Table I. Blood pressures on admission in all patients studied

Blood pressure	Stroganoff		Antihyper- tensive	
readings	No.	1 %	No.	1 %
140/90 -150/100	29	43.9	19	29.7
150/100-160/110	19	28.8	15	23.4
160/110-170/120	6	9.1	14	21.9
170/120-180/130	4	6.1	4	6.3
180/130-190/140	4	6.1	6	9.4
190/140-200/140	1	1.5	5	7.8
200/140-210/140	2	3.0	0	0.0
210/140-220/140	1	1.5	1	1.2
Total	66	100	64	100
Average pressure	15	B/106	162	2/111

Table II. Maternal race distribution

	Stroganoff		Anti- hypertensive	
Race	No.	1 %	No.	1 %
Caucasian	60	90.9	60	93.7
Negro	2	3.1	3	4.6
Other	4	6.0	1	1.7

Table III. Maternal age distribution

Age (years)	Stroganoff		Anti- hypertensive	
	No.	1 %	No.	1 %
15-19	23	34.8	17	26.6
20-24	23	34.8	27	42.2
25-29	11	16.7	5	7.8
30-34	5	7.6	7	10.9
35-39	3	4.6	8	12.5
40-44	1	1.5	0	0
Total	66	100	64	100

Table IV. Maternal gravidity

	Stroganoff		Anti- hypertensive	
Gravidity	No.	1 %	No.	1 %
Primigravida	44	66.6	39	60.9
Gravida ii	8	12.1	5	7.8
Gravida iii	8	12.1	10	15.6
Gravida iv	2	3.0	6	9.3
Gravida v	1	1.7	2	3.1
Gravida vi	3	4.5	1	1.65
Gravida vii	0	0	1	1.65
Total	66	100	64	100

method and 64 with the antihypertensive technique. The analysis of the results of therapy in both groups and the conclusions arrived at represent the basis for this presentation.

Clinical findings

Table I contains the blood pressure readings of patients studied in both groups. It immediately becomes apparent that both groups are somewhat similar in distribution and severity. Closer scrutiny, however, will reveal several more cases in the severe toxemia classification in the antihypertensive group. The maternal race distribution is reported in Table II. It will be noted that over 90 per cent were Caucasian and this very closely parallels the race distribution for all patients delivered in our hospital.

Maternal age was the first factor studied (Table III). The age distribution is essentially comparable in both groups except for minor variations, since the average age for both was 19 years. This distribution merely confirms what has been known and noted by many observers, namely, that toxemia is a disease process found primarily in younger women.

Table IV shows the maternal gravidity in all cases studied. The preponderance of primigravidas in both groups again emphasizes the fact that this disease is found most often in younger women pregnant for the first time.

Diagnostic signs of toxemia present on admission were analyzed to determine which was the most frequent. Hypertension alone, hypertension and albuminuria, hypertension and edema, and a combination of all three were studied. Table V contains our findings in the cases reviewed. It will be noted that in both groups hypertension alone was the most common finding. In the group treated with antihypertensive agents, however, a combination of all three diagnostic signs also appeared in 31.2 per cent of the cases studied. This, plus the fact that there was a slight increase in the number of cases of eclampsia (5 or 7.8 per cent as compared with 4 or 6.0 per cent) in the antihyperten-

Table V. Diagnostic signs on admission

	Stroganoff		Anti- hypertensive	
Diagnostic signs	No.	1 %	No.	1 %
Hypertension	30	45.5	21	32.8
Hypertension and albuminuria Hypertension,	7	10.6	6	9.4
albuminuria and edema Hypertension	8	12.1	20	31.2
and edema	_21	31.8	17	26.6
Convulsive eclampsia	4	6.0	5	7.8
Total	66	100	64	100

Table VI. Total maternal weight gain

Weight	Stroganoff		Anti- hypertensive	
(pounds)	No.	1 %	No.	1 %
0-11	7	10.6	7	10.9
11-15	10	15.2	11	17.2
16-20	11	16.7	16	25.0
21-25	23	34.8	8	12.5
26-30	6	9.1	7	10.9
31-35	4	6.1	3	4.6
36-40	3	4.5	9	14.1
41-45	1	1.5	1	1.6
46-50	0	0	1	1.6
51-55	1	1.5	1	1.6
Total	66	100	64	100

sive therapy group, would tend to suggest an increased severity of toxemia in that group.

Excessive and rapid weight gain has long been considered by many observers as a definite warning sign if not an actual precursor of toxemia. The total maternal weight gain in each of the cases studied was reviewed (Table VI). In the modified Stroganoff group the majority of the cases were in the 21 to 25 pound range and the average gain was 24 pounds. In the antihypertensive group the majority of cases fell into the 16 to 20 pound range with an average weight gain of 19 pounds. An analysis of the figurediscloses a wide range of weight gain with few cases at both extremes. We were surprised, however, to find no real correlation between excessive weight gain and the severity of toxemia.

Table VII shows both the time in weeks

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of gestation when the signs of toxemia appeared and the stage of gestation at which each patient was admitted to the hospital for treatment. By definition only cases of 24 or more weeks' gestation are bona fide and acceptable. It will be noted that in a small number of cases in both groups the toxemia appeared between the twenty-fourth and thirty-fifth weeks. However, the majority of cases in both series occurred at term or in the fortieth week of gestation. In practically every instance the patients were admitted for treatment within one week of the appear-

We were particularly interested in the number of patients in this study with a history either of previous hypertension or of toxemia. As was stated earlier, only those

ance of symptoms.

Table VII. Stage of gestation when toxemia appeared and patient was admitted for therapy

	Strog	onoff	Antihyp	ertensive
Gestation (weeks)		Admission for treatment (No. of patients)		ment (No. of
24 to 26	3	1	1	0
26 to 28	2	0	0	2
28 to 30	4	1	5	1
30 to 32	1	2	2	2
32 to 34	8	1	3	2
34 to 36	5	2	1	1
36 to 38	9	10.	17	14
38 to 40	18	20	12	11
40 to 42	16	29	23	31
42 +	0	0	0	0
Total	66	66	64	64
Average (weeks)	33.7	38.1	35.3	37.8

Table VIII. History of previous hypertension or toxemia

	Modified Stroganoff		Anti- hypertensive	
	No.	1 %	No.	1 %
Previous hyper- tension	4	6	3	4.6
Previous toxemia	7	- 10.6	9	14.0

cases were included in which definitely substantiated superimposed toxemia was found. Table VIII gives the findings in both groups. The actual number of cases of superimposed toxemia is low in both series. Our incidence of recurrent toxemia is in agreement with that of others.

In Table IX is shown a quantitative analysis of the albuminuria in each case, obtained from the patient's catheterized urine specimen immediately after admission. A surprisingly high percentage of both groups were reported as negative on this examination (Stroganoff 59.1 per cent, antihypertensive 50.9 per cent). This, however, is compatible with the incidence of albuminuria as a diagnostic sign as noted previously in Table V. The degree of albuminuria is comparable in both groups, but the average reading appears to be significantly higher in the antihypertensive study group.

The status of the fetus on admission is presented in Table X. In both groups there was one intrauterine death diagnosed prior to admission. As soon as intrauterine fetal death was definitely established, the treatment of both this condition and the accompanying toxemia was undertaken simultaneously.

It is the policy in our hospital to obtain funduscopic examination of all patients with toxemia by a qualified member of the Ophthalmology Service, time and other factors permitting. Table XI discloses the findings in the cases studied. The following functional classification of retinopathy was used:

Grade I. Arteriovenous nicking, slight spasm, translucency, increased reflex stripe.

Grade II. Moderate increase in Grade I findings.

Grade III. Definite hemorrhage and exudates.

Both groups contained a considerable number of cases in which no eye ground findings are recorded on the charts or in which the examination was not done. This appeared to be most common in the modified Stroganoff group composed of the earlier cases studied, when a definite policy regarding this particular examination had not be-

Table IX. Albuminuria on admission

	Modified Stroganoff		Anti- hypertensive	
	No.	1 %	No.	1 %
Negative	39	59.1	32	50.0
Under 50 mg. %	8	12.1	4	6.3
51 to 100 mg. %	9	13.6	12	18.8
101 to 200 mg. %	1	1.5	8	12.5
201 to 400 mg. %	3	4.5	5	7.8
401 to 600 mg. % 601 to 1,000 mg.	4	6.2	3	4.6
%	1	1.5	0	
Over 1,000 mg.				
%	1	1.5	0	
Total	66	100	64	100
Mean	280 n	ng. %	425 n	ng. %
Median	400 r	ng. %	200 n	ng. %
Mode	100 r	ng. %	100 n	ng. %

Table X. Status of fetus on admission

	Modified Stroganoff		Anti- hypertensiv	
	No.	1 %	No.	%
Living	65	98.5	63	96.9
Dead	1	1.5	1	3.1

come firmly established. The others we must attribute either to the fact that delivery was at our subsidiary hospital, where a qualified ophthalmologist was unavailable, or to lack of time or some other pertinent factor that prevented the examintaion from being carried out. We were unable to establish the exact time after admission when each examination was accomplished. In most instances, however, 24 to 72 hours elapsed prior to the initiation of definitive treatment, and the eye grounds were examined during this period. Table XI shows what may be a significant increase in cases with normal funduscopic findings in the antihypertensive group. The rapid release of vasospasm following administration of the antihypertensive drugs presents a physiologic explanation of this finding.

Maternal hemoglobin levels were also studied to see if any correlation was present between either the severity of the disease process or the mode of treatment. An analysis of our findings in both groups is shown in Table XII. It can readily be seen that the two groups are quite similar in distribution, with the majority of cases falling into the 11.0 to 12.9 Gm. per 100 c.c. range.

Uric acid levels in the blood were likewise studied as a possible index of the severity of the toxemia (Table XIII). The range of normal for our laboratory is 3 to 6 mg. per 100 c.c. of serum. The determinations in all of the cases studied in both groups were found to be within this range and no definite conclusions regarding the severity of the toxemia could be made from these data.

As mentioned previously, prompt delivery of the toxemic patient has always been considered a most valuable procedure. More recently, however, with the introduction of antihypertensive drugs, induction of labor has been reserved for a more optimal time when both mother and child would benefit from the termination of the pregnancy. Table XIV summarizes the incidence and method of induction used in this study. In general, induction was used in the modified Stroganoff group when the method itself failed to control the disease process and evacuation of the uterus seemed indicated. On the other hand, inductions were carried out in the antihypertensive group primarily to effect delivery of the fetus at a time more favorable for its survival after the disease had been controlled.

Table XV gives the method of delivery utilized in both groups. The increase in out-

Table XI. Results of funduscopic examination

	Modified Stroganoff		Anti- hypertensive	
	No.	1 %	No.	1 %
Not recorded or				
not examined	43	65.1	21	32.8
Normal	16	24.2	36	56.
Grade I				
retinopathy	4	6.2	2	3.
Grade II				
retinopathy	2	3.0	5	7.1
Grade III				
retinopathy	1	1.5	0	0
Total	66	100	64	100

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Table XIII. Maternal blood uric acid determinations

Uric acid	Stroganoff		Anti- hypertensive	
(mg. %)	No.	%	No.	%
Not done	18	27.3	12	18.4
0-1.9	0	0	0	0
2.0-2.4	6	9.2	6	9.4
2.5-2.9	9	13.7	8	12.5
3.0-3.4	8	11.9	6	9.4
3.5-3.9	8	11.9	13	20.4
4.0-4.4	11	16.8	7	10.9
4.5-4.9	2	3.1	2	3.2
5.0-5.4	3	4.6	5	7.9
5.5-5.9	1	1.5	5	7.9
Total	66	100	64	100
Mean	3.4 m	ng. %	3.7 m	g. %
Median	3.5 m	ig. %	3.5 m	ig. %
Mode	4.3 m	ng. %	3.8 m	g. %

let or low forceps deliveries in the antihypertensive group is in keeping with the current trend of using prophylactic forceps to shorten the second stage of labor. The incidence of 7.7 per cent for midforceps deliveries in the antihypertensive group is higher than average but is not considered significant. It is of interest that the indications for the 3 cesarean sections in the antihypertensive group were entirely obstetric (2 placenta previa, one cephalopelvic disproportion) while both performed in the modified Stroganoff group were for uncontrollable toxemia.

The most important as well as most significant finding in this study is illustrated in Fig. 1. This is the time interval from initiation of therapy to the return of the blood

Table XII. Maternal hemoglobin determinations

Hemoglobin	Stroganoff		Anti- hypertensive	
(Gm. %)	No.	1 %	No.	1 %
8.0- 8.9	0	0	1	1.6
9.0- 9.9	4	6.1	4	6.3
10.0-10.9	8	12.1	14	21.9
11.0-11.9	17	25.8	13	20.3
12.0-12.9	17	25.8	15	23.4
13.0-13.9	10	15.1	12	18.7
14.0-14.9	7	10.6	3	4.7
15.0-15.9	3	4.5	2	3.1
Total	66	100	64	100
Mean	11.9	Gm.	11.7	Gm.
Median	12.0 Gm.		11.5	Gm.
Mode	12.5	Gm.	12.0	Gm.

pressure to near normotensive levels. The toxemia in the antihypertensive group was controlled in an average of 10.2 hours with the most severe case requiring therapy for 10 days. On the other hand, the average time required to control toxemia by the modified Stroganoff method was 137.7 hours with at least 3 cases which never responded entirely satisfactorily. We feel the rapidity with which the antihypertensive drugs control this complication is a definite asset, because the danger of convulsions is for the

most part removed and the normal physiologic state state of pregnancy is allowed to continue until a predetermined and safe time and method of delivery can be selected.

Table XVI merely lists the complications of labor and delivery encountered in both groups. Placenta previa was encountered twice in the antihypertensive group and was treated by cesarean section with delivery of viable infants in both cases. The relationship of premature labor and delivery will be discussed later, along with the analysis of fetal and neonatal statistics.

The weights of all infants in the study were analyzed to evaluate the incidence of maturity at time of delivery. This information is contained in Fig. 2. As will be noted, the majority of the infants in both groups weighed between 3,000 and 3,500 grams at birth. The average weight in the antihypertensive group was 3,350 grams as compared with 3,050 grams in the modified Stroganoff group. This indicates a small margin of maturity for the former, if weight alone is considered the criterion. When fetal age in terms of weeks of gestation is considered, however, very little difference is noted. Fig. 3 shows graphically the duration of gestation for both groups at the time of delivery. The average age for the modified Stroganoff group is 38.8 weeks and for the antihyper-

Table XIV. Method of induction

Method of	Stroganoff		Anti- hypertensive	
induction	No.	%	No.	%
None	42	65.1	36	56.2
Medical (intra- venous Pitocin)	16	24.2	13	20.3
Surgical (rupture of membranes				
only)	1	1.5	8	12.5
Combined	7	9.0	7	10.9
Total inductions	24	34.7	28	43.7

Table XV. Method of delivery

Method of	Stroganoff		Anti- hypertensive	
delivery	No.	1 %	No.	1 %
Spontaneous				
(vertex)	37	56.2	28	42.4
Outlet or low				
forceps	22	33.3	29	43.9
Mid forceps	3	4.5	4	7.7
High forceps	0	0	0	0
Cesarean section	2	3.0	3	4.5
Breech assist	2	3.0	1	1.5
Total	66	100	65*	100

*One set of twins.

tensive group 39.3 weeks. This difference does not appear to be significant.

Fetal and neonatal statistics are reported in Table XVII. The reversal in ratio of males to females in the two groups is interesting but not significant. The incidence of prematurity was approximately equal in both groups, a fact which was certainly not anticipated. The idea had been strongly entertained that any method of therapy designed to restore the normal physiologic status of a pregnancy would likewise allow it to continue longer and thus reduce prematurity. This was not found to be the case in this study, and the explanation probably is the fact that the majority of cases of toxemia in both groups appeared near term so that little if any more gestation time was actually required. Fetal age and weight analysis appear to confirm this impression.

An analysis of the stillbirths in each group was found interesting. There were 3 (4.5 per cent) in the modified Stroganoff group as compared with one (1.6 per cent) in the antihypertensive group. It will be remembered that there was one intrauterine fetal death diagnosed on admission in each group. From this it is evident that in 2 (3.0 per cent) of the cases in the modified Stroganoff group intrauterine fetal death occurred after admission and while the patients were under therapy. It is felt this places considerable emphasis on the physiologic advantage afforded the infant in all cases managed with antihypertensive drugs and may be significant.

In analyzing the neonatal deaths in the study we find that the incidence is approximately equal in both groups and of no significance.

A comparison of the combined neonatal

Table XVJ. Complications of labor and delivery

Complication	Stroganoff	Antihyper- tensive
None	53	52
Placenta previa		2
Abruptio placentae	2	
Premature labor and		
delivery	10	11
Uterine inertia	. 1	
Occiput posterior or		
transverse	2	
Breech	1	
Twins		1
Amnionitis	1	
Laceration of pelvic		
floor	2	
Retained placenta		1
Postpartum hemorrhage		1

Table XVII. Fetal and neonatal statistics

	Stroganoff		Anti- hypertensive	
	No.	%	No.	%
Male	28	42.4	36	54.5
Female	38	57.6	30	45.5
Premature	10	15.1	11	16.1
Term	56	84 9	55	83.3
Living	61	92.5	62	93.9
Stillborn	3	4.5	1	1.6
Neonatal death	2	3.0	3	4.5
Combined fetal and neonatal				
deaths	5	7.5	4	6.1

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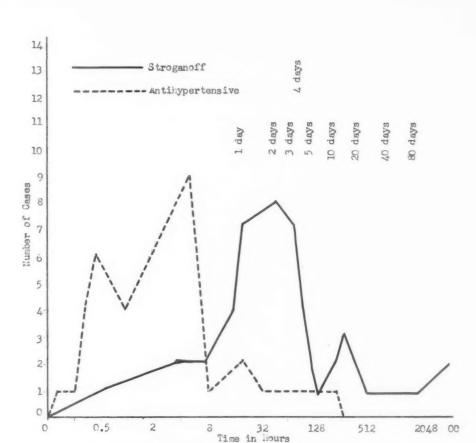


Fig. 1. Interval from initiation of treatment to return of normal blood pressure.

Stroganoff

Mean

137.7 hours

Median

48 hours

10.2 hours

3 hours

hours

and fetal deaths in both groups revealed an insignificant decrease from 7.5 per cent for the modified Stroganoff method to 6.1 per cent for those treated with antihypertensive medications. These figures are considered comparable to the incidence reported from several other sources by investigators^{16, 18, 22, 43, 45} using similar methods of toxemia management.

Mode

Maternal statistics were likewise reviewed (Table XVIII). Not only was there an increase in the number of uncomplicated cases in the antihypertensive group but a concomitant decrease in morbidity from 22.7 per cent in the modified Stroganoff group to 12.5 per cent in the antihypertensive group, which we feel is quite significant. This decrease is likewise reflected in the maternal mortality rate which dropped from 3.1 per cent for the

modified Stroganoff method to none for the antihypertensive group.

5

hours

Also contained in Table XVIII are the maternal blood pressure readings taken immediately after delivery and on the day of discharge from the hospital. It will be noted that 95.9 per cent of the patients treated with antihypertensive drugs had normotensive blood pressure readings at the time of discharge despite the fact that 46.8 per cent were in the severe toxemia range at the time of admission. This we feel is highly significant and reflects a more physiologic and successful method of management.

Summary

A review of the historical background of the treatment of toxemia of pregnancy has been presented. The evolutionary process

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Table XVIII. Maternal statistics

	Stroganoff		Anti- hypertensiv	
	No.	1 %	No.	%
Normal	49	74.2	56	87.5
Morbidity	15	22.7	8	12.5
Mortality	2	3.1	0	0
Normal blood pressure follow- ing delivery Elevated blood	34	51.5	48	75.0
pressure follow- ing delivery	32	48.5	16	25.0
Normal blood pressure on discharge	44	60.6	61	95.9
Elevated blood pressure on				
discharge	22	39.4	3	4.1

leading to the development of present-day management is outlined along with the rationale of treatment used.

During the 3 year period from July 1, 1953, to June 30, 1956, a total of 13,771 pa-

tients were delivered at the U. S. Naval Hospital, San Diego, California. Of this number 693 cases were coded as toxemia of pregnancy or a variant thereof. Utilizing the criteria set down by the American Committee on Maternal Welfare, 130 cases of bonafide toxemia of pregnancy were selected for study. Cases not meeting these criteria were excluded.

The 130 acceptable cases were divided into two groups on the basis of the method of management. The first group of 66 cases was managed by the modified Stroganoff regimen, with utilization of the principles of heavy sedation, parenteral magnesium sulfate, hypertonic intravenous dextrose in water, and quiet, darkened surroundings. The second group of 64 cases was managed with antihypertensive medications orally and/or intravenously, parenteral magnesium sulfate, and a darkened, quiet environment.

Cases in both groups were studied in regard to numerous fetal and maternal labora-

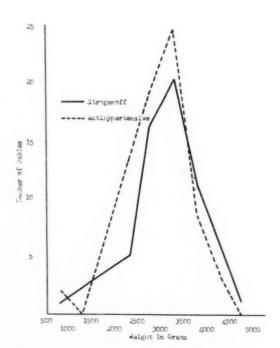


Fig. 2. Fetal weights at time of delivery.

Stroganoff Antihypertensive

Mean 3,050 Gm. 3,350 Gm.

Median 3,001 Gm. 3,110 Gm.

3,250 Gm.

3,025 Gm.

Mode

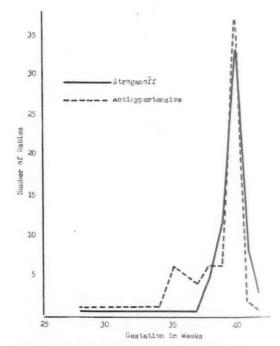


Fig. 3. Duration of gestation at time of delivery.

Stroganoff
Mean 38.8 weeks 39.3 weeks
Median 40 weeks 40 weeks

weeks

40

weeks

40

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tory and clinical data. A marked decrease in the interim time required to control the pathologic processes of toxemia was noted with management with antihypertensive agents. There was no great decrease in combined fetal and neonatal mortality but maternal morbidity and mortality were noted to be significantly reduced by the use of antihypertensive drugs in the treatment of severe toxemia of pregnancy.

Conclusions

From an analysis of the foregoing report the following conclusions seem justified:

- 1. Toxemia is found most frequently in younger primigravidas.
- 2. Excessive weight gain noted in this study, although possibly a precursor of toxemia, was not directly related to the severity of the disease process.
- 3. Although toxemia by definition is manifested by the appearance of symptoms during or after the twenty-fourth week of gestation, the majority of cases in our study occurred during or after the thirty-fifth week.

- 4. The use of antihypertensive medications in the treatment of toxemia of pregnancy significantly decreases arteriolar vasospasm as reflected by the eye ground findings and the fall of blood pressure to near normotensive levels.
- 5. Antihypertensive treatment of toxemia eliminates the need for cesarean section as a means of terminating a pregnancy except for purely obstetric indications.
- 6. The use of antihypertensive medications significantly reduces the interim time required for the return of blood pressure to safe and normotensive levels.
- 7. When antihypertensive medications were used in the treatment of toxemia an apparent decrease in stillbirths was noted.
- 8. Treatment of toxemia with antihypertensive drugs did not significantly decrease the combined incidence of fetal and neonatal mortality in this study.
- 9. Maternal morbidity and mortality rates were significantly decreased in the group treated with antihypertensive medications in the management of severe toxemia of pregnancy.

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Natural resistance to infectious diseases during pregnancy: possible relationship to serum properdin concentration

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SINCE the recent discovery of properdin by Pillemer and co-workers,1 numerous studies have demonstrated its role in the antibacterial, antiviral, and antiprotozoal activity of fresh serum. Because this unique beta euglobulin in the presence of complement and magnesium ions exerts its antimicrobial effects in the absence of specific antibodies, properdin and the properdin system are now considered an important component of natural immunity or natural resistance to infection. Experimental alterations of properdin levels in animals have been shown to affect materially their ability to resist infection. It is also probable that recently demonstrated variations in serum properdin levels in various age groups, various races, and perhaps in certain disease states will also bear a significant relationship to natural resistance to infection in humans.²

One of the conditions which has long been felt to alter natural resistance to infections among humans is pregnancy.3 Such a decrease in natural resistance to acute infections could be manifested in one or both of two ways. The pregnancy could change the usual course of the disease, or the disease itself could alter the normal course of the pregnancy, that is, could produce abortion, premature delivery, stillbirth, or fetal malformation. Although the pregnant woman probably does not have a decreased natural resistance to all acute infections, there is a considerable body of evidence in the literature to support the thesis that natural resistance to certain infectious diseases is definitely decreased.

Diseases where the natural course may be altered by pregnancy

Decreased resistance to certain infectious diseases is found to be manifested by increased susceptibility to infection, morbidity, tendency toward disseminated infections, and mortality after infection is acquired.

Bacterial infections. Studies of typhoid fever epidemics leave little doubt that the

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This investigation was supported in part by the Research and Development Division, Office of the Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-694, and by National Institutes of Health, United States Public Health Service, Graduate Training Grant No. 2E-52. disease is more serious when acquired during pregnancy unless prompt treatment is instituted.4,5 In the preantibiotic era, Villarama and Gelang4 found a 15 per cent maternal mortality due to typhoid, which is greater than in nonpregnant patients. Pregnancy also apparently causes a decrease in resistance to Vibrio cholerae. During a cholera epidemic in Germany in 1894, Schütz⁶ reported a 57 per cent maternal mortality due to cholera, which he stated was much greater than that found in nonpregnant women. Infection due to Pasturella pestis during pregnancy carries a bad prognosis for both mother and child, producing a maternal mortality and fetal mortality of 80 per cent and 88 per cent, respectively.7.8 Pregnancy also adversely affects the course of diphtheria since there seems to be an increased tendency toward laryngeal involvement.9

There are several other bacterial diseases which are probably related to decreased natural resistance during pregnancy, but the evidence for this causal relationship is not conclusive. In a study of bacteroides infections, Carter and associates¹⁰ showed that fatal infection with bacteroides was frequently associated with a variety of debilitating conditions, as well as with pregnancy, but in groups with no associated illnesses there were no deaths. Although pseudomonas septicemia is a rare condition in the nonpregnant human, several cases have been reported occurring during pregnancy or in the immediate postpartum period.11 Almost all fatalities during epidemics of shigella dysentery have occurred in children less than 5 years of age, in the aged, or in people with debilitating diseases. 12, 13 Manson-Bahr, however, did state that the mortality due to shigella infections was also increased during pregnancy.13

There seems to be little doubt that the incidence, morbidity, and mortality due to pyelitis is much greater during pregnancy than in nonpregnant states. 14-16 The most frequently found organism in pyelitis of pregnancy is *Escherichia coli*, but other organisms such as micrococcus species, pseu-

domonas species, aerobacter species, proteus species, and various streptococci have been isolated. Although most authorities agree that the most important predisposing factors were urinary and bowel stasis, especially factors related to ureteral obstruction, there is also some evidence to indicate that immune factors may be important.¹⁶

Before the era of antibiotics, bacterial pneumonia produced a high rate of maternal mortality.^{3, 8, 9} Streptococcal infection was also a serious complication,³ and Torrance showed that pregnant white mice had a higher mortality rate following intraperitoneal inoculation of streptococci than had nonpregnant mice.¹⁷

Viral infections. A recent smallpox epidemic in Bombay18 confirmed earlier investigations indicating that the purpuric and more virulent fatal forms of the disease are seen more commonly during pregnancy. 19, 20 Although Roth²¹ found no increase in maternal mortality due to infectious hepatitis, the investigations of large epidemics of this disease in India showed a significantly higher mortality among pregnant women than among nonpregnant women of the same age groups.22, 23 They also found that the incidence of the disease was almost twice as great in the pregnant population. Investigations of the 1919 influenza pandemic by Harris²⁴ revealed that more than 50 per cent of the pregnant women who acquired influenza developed pneumonia, and, of these, there was a 50 per cent mortality. Other studies revealed an over-all mortality rate due to influenza to be 23.5 per cent in men, 12.5 per cent in women, and 45.9 per cent in pregnant women.8 Recent analyses of the epidemics of Asian influenza in New York²⁵ and Boston²⁶ revealed that not only was the greatest mortality among pregnant women and people with rheumatic heart disease, but also that one third of the fatalities of women between the ages of 14 and 49 were in those who were pregnant. Early studies of the effect of pregnancy on the course of rubeola by Klotz27 and later by Esch²⁸ agreed that the mortality rate was considerably increased when rubeola was 1961

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acquired during pregnancy. Pregnant women also seem to be more susceptible than nonpregnant women to the common cold and other acute viral upper respiratory infections.3

The influence of pregnancy upon the incidence and course of poliomyelitis has stimulated a considerable amount of study. Most investigators agree that there is probably a greater incidence of poliomyelitis in pregnant women, with the incidence of infection being greatest during the second trimester.29-31 There is disagreement, however, as to whether pregnancy increases the morbidity or mortality of poliomyelitis, since several studies have presented evidence demonstrating either no differences,32 increased mortality but the same incidence of paralysis, 33, 34 or definitely increased mortality and incidence of bulbar and spinal paralysis35 in pregnant as compared to nonpregnant women.

Protozoal infections. Although an earlier report revealed no increased morbidity due to malaria during pregnancy,36 Wickramasuriya37 found that there was a higher incidence of cerebral involvement, reactivation of latent infections, and intensification of existing attacks, as well as toxemia and eclampsia when malaria was associated with pregnancy. Although toxoplasmosis is seen more often as the cause of stillbirths and fetal deformities, John³⁸ felt that it may frequently be present as an asymptomatic disease in adults, and he was of the opinion that pregnancy could reactivate a latent infection which had existed previously in the nonpregnant woman. The observation that asymptomatic female carriers may develop symptomatic amebiasis during pregnancy is consistent with the view that pregnancy decreases resistance to this disease. 89

Chronic infections. There have been a great number of divergent opinions concerning the effect of pregnancy upon the natural course of tuberculosis, but at the present time statistical data do not show differences between pregnant and nonpregnant women with this disease, although women with tuberculosis are still advised

not to become pregnant.40 Some of the recent reviews41-43 of this subject pointed out that perhaps the reason for the difficulty in interpreting the effects of pregnancy upon the course of tuberculosis is that, first, tuberculosis is a chronic and relapsing disease with a slow evolution, and with such a disease it is difficult to evaluate the effect of the pregnancy itself, which may only represent a short period during the normal course of the disease. Second, the prognosis and course depend upon numerous factors, such as the extent of the disease, the activity of the disease, the adequacy of care, and many other circumstances in addition to pregnancy, so that evaluation of any one single factor would become quite difficult. In addition, the available statistics may be heavily weighted because the more seriously ill patients would probably not become pregnant, and would thus be included in the nonpregnant group.

Although Eastman³ stated that the primary lesion of syphilis may be more extensive when acquired during pregnancy, Stokes44 wrote that most manifestations of syphilis are less apparent when associated with pregnancy. The difficulty in interpreting the influence of pregnancy upon the natural course of syphilis is probably due to the same reasons as those previously stated in the discussion of tuberculosis.

Diseases which alter the course of pregnancy or cause fetal damage

Not only can pregnancy affect the natural course of a number of diseases, as evidenced by alterations in incidence and maternal morbidity and mortality, but, in addition, certain diseases can alter the pregnancy as manifested by spontaneous abortions and premature deliveries, and can also cause fetal damage, as manifested by stillbirths and fetal malformations. In the preantibiotic era, scarlet fever and bacterial pneumonias were known causes of premature labor and abortion.3 Erysipelas due to hemolytic streptococci was not only dangerous because of possible development of puerperal infection, but it could actually be-

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Table I

Group	No. of in- fections reported	No. of dis- seminations reported	No. of deaths reported
White	31	8	, 7
Negro	11	11	11
Chinese	1	1	1
Mexican	2	1	0
Total	45	21	19

come invasive, causing transplacental infection and death of the fetus. Villarama and Gelang4 reported that there was a 60 to 80 per cent incidence of abortion and premature delivery due to typhoid fever during pregnancy. During the cholera epidemic in 1894, reported by Schütz,6 there was an abortion rate of 54 per cent and a large number of stillbirths. Bacterial dysentery, especially due to the shigella organisms, seems to increase the rate of abortion,13 and pyelitis of pregnancy due to a number of other gram-negative organisms is also considered a danger to the fetus.16 The case report of pseudomonas septicemia during pregnancy was also associated with stillbirth.11

Among the viral diseases, variola,45 infectious hepatitis,21,23 influenza,8,24 mumps,46 rubella,47,48 and rubeola27,28 have also been shown to increase the incidence of spontaneous abortion, fetal injury, or fetal death. The incidence of fetal abnormalities caused by rubella infections during the first trimester is well established.47, 48 Campbell49 reported that influenza in early pregnancy did not influence the rate of stillbirth or fetal abnormality, but other studies revealed an abortion rate of 26 per cent which increased to 52 per cent if pneumonia supervened.8, 24 Horn32 reported a 22 per cent fetal loss due to infection of pregnant women with poliomyelitis. Among the protozoal diseases there is not much disagreement that malaria^{36, 37} and toxoplasmosis³⁸ can cause death or damage to the fetus, and amebiasis39 may also increase the tendency to abort.

As a rule, tuberculosis in the pregnant

woman does not affect the child, but occasionally the disease may be transmitted in utero so that a child is born with congenital tuberculosis. On the other hand, the devastating effect of untreated syphilis acquired during pregnancy on the rate of abortion, premature delivery, and fetal abnormalities is a well-established fact. 51-53

Effect of pregnancy on resistance to coccidioidomycosis

An important disease in which the course and severity seem to depend to a considerable extent upon the natural resistance of the infected host is coccidioidomycosis. This may be the explanation for the incidence of dissemination among Negroes where the rate of dissemination of coccidioidomycosis is 10 to 15 times greater than that of normal white patients of the same age group.54,55 On the basis of the cases reported since 1941, infection with coccidioidomycosis during pregnancy also carries a much greater danger of dissemination, even in white women, than in nonpregnant women of the same age group. Since 1941, 45 cases of coccidioidomycoses during pregnancy have been reported in the literature.* Of these 45 cases, there have been 21 instances of dissemination and 19 deaths. 56-62 In addition, spontaneous abortions, threatened abortions, stillbirths, premature delivery, or placenta previa occurred in 21 instances, but coccidioidomycosis did not directly cause fetal malformation. Cohen⁶⁰ and others^{56, 59, 61, 62} have demonstrated that, although the placenta may be infected, Coccidioides immitis is probably not able to cross the placental barrier and cause fetal infection.

Among the various racial groups, the rate of disseminations and fatalities among pregnant women is seen in Table I.

Although the number of cases reported is small, there is certainly good evidence that there is a markedly increased tendence toward dissemination of coccidioidomycosis during pregnancy, and this is apparently.

^{*}Two other nonfatal cases were mentioned without further details.*2

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true for white patients as well as nonwhites. Confirmation of this hypothesis should be forthcoming if the estimate of Vaughan and Ramirez⁵⁹ that infection with coccidioidomycosis in the endemic areas occurs in one in 1,000 pregnancies proves to be true.

The trimester during which infection was contracted or diagnosed in the reported cases and in how many of these dissemination or death occurred is listed in Ta-

These data seem to indicate that the danger of dissemination is greatest when coccidioidomycosis is acquired during the third trimester of pregnancy, but this may be more apparent than real when one considers the natural course of the disease.54,55 Since initial infection may occur weeks to months before evidence of infection becomes apparent, coccidioidomycosis acquired during pregnancy might not become apparent until the third trimester, although the initial infection could well have occurred in the first or second trimester. This is quite probable in several of the case reports where sufficient information to calculate the approximate date of infection is provided.

Although the cause of this apparently decreased resistance to infection during pregnancy is unknown, it is quite possible that variations of one or more components of the properdin system during pregnancy are important factors. If a decrease in serum properdin concentration occurred during pregnancy, one would expect a corresponding decrease in maternal resistance to infection, causing pregnant women to be more susceptible to certain infections, and the course of the infections would be more sever. Changes in the mother, produced by these infections, could also account for the frequency of spontaneous abortion, premature delivery, stillbirth, and fetal malformation. In addition, the lowering of natural resistance in the mother might not be enough to produce clinical changes in her, but could allow for transplacental infection of the fetus. Since earlier studies have

Table II

	Prior to preg- nancy	First tri- mester	Second tri- mester	Third tri- mester	Post partum
Infection Dissemi-	8	14	6	16	1
nation	2	3	3	12	1
Death	2	3	2	11	1

shown properdin concentrations in cord blood to be very low (0 to 38 units per milliliter), fetal malformations or death due to transplacental infection would not be unexpected.63

To test the hypothesis that decreased resistance to infection during pregnancy may be related to the properdin system, serum properdin concentrations of pregnant women during various stages of pregnancy were determined and compared to levels of normal humans of the same age group.

Materials and methods

Serum properdin concentrations of pregnant women were determined from blood samples drawn at the time of their initial prenatal laboratory studies. A single blood sample was obtained from 125 pregnant women between the ages of 17 and 40. Of these, 34 were in the first trimester of pregnant (white 31, Negro 1, Mexican 2); 48 were in the second trimester of pregnancy (white 44, Negro 2, Mexican 1, Oriental 1); and 43 were in the third trimester of pregnancy (white 35, Negro 5, Mexican 3). For purposes of this study, the trimesters were divided as follows: first trimester, first to thirteenth week; second trimester, fourteenth to twenty-sixth week; third trimester, twenty-seventh to fortieth week or term.

The serum was separated from the blood samples by centrifugation at 4,000 r.p.m. for a period of 10 minutes after the blood had been allowed to clot in the refrigerator. The serum was then stored in a mechanical freezer at -20° C. until the actual properdin determinations were made. The concentrations of properdin in the sera were determined according to the method described by McNall⁶⁴ in 1957. This method gives much more consistent and reproducible results than previously described methods of properdin assay. The unitage used in this method also gives a wider spread among the individual values making statistical analysis and comparisons more readily discernible.63, 64 After the determinations were completed, the individual properdin values were divided into trimester groupings. Arithmetic means, standard errors of the means, and standard errors of differences of the means were calculated. Significance levels and T values for differences between the means among the three trimester groups and normals were also determined.

The determinations of properdin concentration in pregnant women in this study were analyzed with reference to the properdin concentration of normal humans assayed in previous investigations. A control

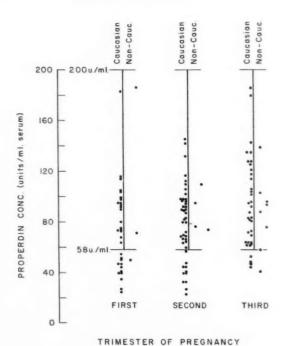


Fig. 1. Distribution of individual properdin determinations during each trimester of pregnancy superimposed on range of normal for white women of the same age group. The bars represent the range of values in normals. Each dot represents a single determination in a pregnant woman. White patients are arranged to the left of the bar and non-whites to the right.

group of normal women was not used in this study since a significant number of such determinations had been done previously. Because of the reproducibility and standardization of the properdin assay enployed in this study, as well as the controls inherent in the method, there is no loss of reliability when determinations in one series are compared to those of a later or earlier series.

In addition to properdin concentrations, other data which could have been significant were recorded for each of the pregnant women studied. These included number of previous pregnancies, number of term deliveries, number of spontaneous abortions and premature deliveries, ABO blood groupings, and Rh factors. Since only normal pregnant women were included in the studies, the routine laboratory work, including complete blood count, urinalyses, and serologic tests for syphilis were normal in all of the patients studied.

Results

The individual serum properdin concentrations from each of the pregnant women are plotted in Fig. 1. The properdin determinations are grouped according to the trimester during which the serum was obtained and are superimposed on the range of values of properdin in normal white women, from age 17 to 40.2, 63, 65 Because previous studies have shown racial differences,2 the properdin concentrations for the white and non-white pregnant women have been separated on the chart. In general, the properdin concentrations of the pregnant women tended to fall in the low range of the normal or below the range of normal for white women of the same age group. Of 31 white patients in the first trimester of pregnancy, the properdin le els ranged from 25 to 183 units per milliliter of serum, with a mean of 73.7 units per milliliter; of 44 white women in the second trimester, the properdin values ranged from 23 to 146 units per milliliter of serum, vith a mean of 77.3 units per milliliter; and of 35 white women in the third trimester of

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Table III. Comparison of serum properdin concentrations (white women, age 17 to 40)

Group	No. of determi- nations	Mean con- centration (units/ ml.)	Range (units/ml.)	Standard errors of mean (units/ ml.)	% of determina- tions less than 58 units/ml.	% of determinations greater than 130 units/ml.	T value	P value: level of signifi- cance
Normal	39	110.1	58-200	±6.43	2.5	30.8		
Trimester I	31	73.7	25-183	±5.91	38.7	3.2		
Trimester II	44	77.3	23-146	±3.95	25	6.8		
Trimester III	35	94.9	45-186	±6.35	11.4	14.3		
Differences betw	een the me	ans of the g	roups					
I and III		21.2					2.46	2%
II and III		17.6			2.34			3%
I and II		3.6					0.505	Not signifi-
I and Normal		36.4					4.17	1%
II and Normal		32.8					3.02	1%
III and Normal		15.2					1.668	10%

pregnancy, the properdin values ranged from 45 to 186 units per milliliter of serum, with a mean of 94.9 units per milliliter. When the non-white women are included in the 3 trimesters, the ranges and mean values are approximately the same. The range of properdin concentrations for normal white women of the same age group are from approximately 58 to 200 units per milliliter, with a mean of 110.1 units per milliliter.*

A summary of the statistical analysis and comparison of these data is given in Table III. This analysis reveals that the mean serum properdin concentrations during the first and second trimesters are lower than that during the third trimester, well within the 5 per cent significance level, and there is no significant difference between the means of the first and second trimesters. In addition, the mean serum properdin concentration in normal white women is possibly significantly higher than that in pregnait women in the third trimester, being within the 10 per cent level of significance. The mean properdin concentrations of normal white women, however, is definitely significantly greater than that during the first and second trimesters, being within the 1 per cent level.

The contrast between the properdin concentrations during the 3 trimesters of pregnancy and normals is made more apparent by a comparison of the number of determinations outside the range of 58 to 130 units per milliliter. Of the normals, only one determination, or 2.5 per cent, was below 58 units per milliliter, while among similar numbers of pregnant women there were 38.7, 25, and 11.4 per cent below 58 units per milliliter in the first, second, and third trimesters, respectively. Of the normal, 30.8 per cent of the properdin concentrations were above 130 units per milliliter, while among the pregnant women, only 3.2, 6.8, and 14.3 per cent were above that level in the first, second and third trimesters, respectively.

Similar statistical analyses did not reveal significant differences between properdin levels among pregnant women in the various A, B, O blood groups and Rh groups, nor did they show any correlation with number of previous pregnancies, previous term deliveries, premature deliveries, or spontaneous abortions. Because of the relatively few non-white pregnant women studied, no definite conclusions can be drawn regarding the properdin values among them.

There was only one determination (40 units per milliliter) below 58 units per milliliter in the normal group.

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Table IV. Pathogenic microorganisms related to natural immunity in pregnancy and/or influenced by properdin

Microorganisms producing disease whose natural course may be altered by pregnancy	ducing disease rse may be gnancy	Microorganisms which may alter course of pregnancy (abortion or premature delivery)	may alter bortion or try)	Microorganisms which may produce fetal damage (stillbirth or fetal malformation)	hich may e (stillbirth ration)	Microorganisms influenced in vitro or in vitro or in vivo by properdin	enced in vitro or properdin
Organism	References	Organism	References	Organism	References	Organism	References
Bacteria		Bacteria		Bacteria		Bacteria	
Salmonella typhosa	4,5	S. typhosa	4 4	77	¥	S. typhosa	66, 67, 75, 76, 77
Pasturella bestis	7.8	P. bestis	7.8	V. cholerae	0	Bacterium subtilis	66, 67
Corynebacterium							
diphtheriae	6						
bacteroides species	10					-	rr 2r 2r 23
Pseudomonas species	11			Pseudomonas	11	Pseudomonas	00, 01, 13, 10, 11
Shigella species	13	Shioella species	65	sheries		sheries	
Bacterial pneumonia	3 8 9	Bacterial pneumonia	3.8.9			Shigella	66, 67, 75, 76, 77
Streptococcus	3, 17	Streptococcus species	8	Streptococcus	8	Klebsiella pneu-	75, 76, 77, 78
species				species		moniae	
Pyelitis	14, 15, 16	Pyelitis	14, 15, 16	Pyelitis	14, 13, 16	200	44 34 34 43 33
Escherichia coli		E. coli		E. coli		E. cott	11,01,61,10,00
Proteus species		Aerobacter species		Aerobacter		rroteus species	00, 01, 73, 70, 71
species		veronaciei species		species			
Micrococcus		Micrococcus		Micrococcus		Micrococcus	89
species		species		species		species	
Viruses		Viruses		Viruses		Viruses	
Variola	18, 19, 20	Variola	4,5	Variola	45	Newcastle's dis-	69
		;		- :	,	ease	6
Hepatitis	22, 23	Hepatitis	21, 23	Hepatitis	1, 23	E. coli bacteri-	70
Influenza	6	Influenza	8. 24			Influenza	72
Asian influenza	25, 26	Mumps	46	Mumps	46	Herpes simplex	71
Rubeola	27, 28	Rubeola	27, 28	Rubeola	27, 28		
Poliomyelitis	29-35	Poliomyelitis	32				
Common cold	3	Rubella	47, 48	Rubella	47, 48		
Protozoa		Protozoa		Protozoa		Protozoa	
Malaria species	37	Malaria	36, 37		2		
Toxoplasma gondii Endamoeba his- tolytica	388	T. gondii E. histolytica	38	T. gondii	38	T. gondii	73,74
Fungi		Funoi				Fungi	
t we car don'the	36-62,86	C. immitis	29-92			C. immitis	37.91
mitis							

In this study, the values for these women seemed to distribute themselves within the range of the white women studied in each of the trimester groupings.

Comment

In general, the data presented indicate that serum properdin concentrations in a large number of pregnant women in all stages of pregnancy are in the low normal or below normal range of properdin concentrations for white women in the same age group. In addition, the serum properdin levels in the first and second trimesters of pregnancy are significantly lower than that in the third trimester. The differences in properdin concentration between the first, second, and third trimesters may be even greater than apparent when one takes into consideration the hemodilution and increased plasma volume which is greatest during the later stages of pregnancy. Although this study demonstrates that there is a net over-all decrease in the level of properdin within the 3 trimester groups studied, the determination of whether or not this decrease occurs in each individual would require further long-term serial studies in humans and experimental animals.

Although there is no direct evidence proving that the decreased serum properdin concentrations in pregnant women play a major role in their decreased resistance to certain infections, such a hypothesis is certainly compatible with findings of experimental investigations, both in vitro and in vivo. Properdin has been found essential for in vitro lysis by serum of organisms such as Escherichia coli, proteus species, Shigella dysenterae, Bacillus subtilis, and Salmonella species. 66, 67 Although properdin has been found ineffective against many gram-positive bacteria, Nanni⁶⁸ has demonstrated that sera adsorbed with zymosan had a decreased opsonic activity against micrococcus but regained its opsonic activity when the eluate was replaced. Other in vitro studies have shown properdin to be effective in the inactivation of the viruses of Newcastle's dis-Escherichia coli bacteriophage, 70 herpes simplex,71 and influenza.72 Properdin also appears to be involved in the inactivation of Toxoplasma gondii.78, 64

When serum concentrations of properdin are raised or lowered experimentally, there are significant changes in the ability of experimental animals to resist infection. Thus, when serum properdin levels are raised by preparatory injections of zymosan,75 bacterial lipopolysaccharides,76 and tissue polysacccharides,77 resistance of experimental animals to challenge injections of Salmonella typhosa, Klebsiella pneumonia, proteus species, E. coli, and pseudomonas species is increased. Ross⁷⁸ also was able to protect mice against an ordinarily lethal challenge of K. pneumoniae by injecting human properdin 4 hours before or two hours after injection of the bacteria. In vivo studies by Wahlig,79 and other studies in this laboratory65 have shown a possible relationship between the properdin system and tuberculosis. In addition, Landy and Pillimer⁷⁶ showed that although the properdin levels of control animals fell after a challenge injection of various bacteria, animals previously injected with bacterial lipopolysaccharide maintained a normal or above normal properdin concentration despite the infection. Conversely, animals whose serum properdin has been lowered by large doses of polysaccharide,75 cortisone,80 or roentgen irradiation80,81 are less resistant to infection and have lowered bactericidal activity of their sera. Serum properdin levels in humans are also lower in diseases such as peritonitis, burns, septic and hemorrhagic shock, 82, 83 Hodgkin's disease,84 cancer,84,85 and systemic lupus erythematosus,2 diseases which are commonly considered to cause "lowered resistance."

The apparently greater incidence of fatal dissemination in pregnant women who acquire coccidioidomycosis during the third trimester is not entirely consistent with the finding of lower serum properdin concentration in the first and second trimesters of pregnancy. This apparent inconsistency might be reconciled by consideration of the natural course of coccidioidomycosis where

initial infection may occur weeks to months before there is evidence of infection or dissemination.^{54, 55, 86} In any event, from the data presented in this study, the serum properdin level is probably low enough in all 3 trimesters to be compatible with lowered resistence to coccidioidomycosis throughout pregnancy in a significant number of these women.

The relationship between serum properdin and resistance to coccidioidomycosis is supported by a large body of circumstantial evidence. It is generally accepted that Negroes are more liable to develop disseminated coccidioidomycosis after primary pulmonary infection, and evidence has been presented which may explain, at least in part, this increased susceptibility on the basis of markedly lower properdin levels of some individuals of this race.2, 63 It is also well known that desert mice and other desert rodents are relatively susceptible to the disseminated form of this disease, 87 whereas dissemination of coccidioidomycosis is not known in horses, sheep, and cattle.88 The properdin levels of the former group of animals are much lower than those of the latter group.89

When mice were infected with large doses of Coccidioides immitis, there was a subsequent depression of serum properdin concentrations, and low properdin levels were also found in humans with disseminated coccidioidomycosis.90 On the other hand, when the properdin concentrations of mice were increased by preparatory injections of suspensions of a moderate amount of powdered inulin, the death rate following the challenge with C. immitis was significantly less than in the controls.91 Conversely, lowering properdin levels by injection of large amounts of inulin caused significantly increased death rates following challenge with C. immitis.

A comparative list of pathogenic micro organisms possibly related to pregnancy and/or maternal natural immunity and serum properdin is presented in Table IV.

Although the mechanism by which properdin falls during pregnancy is not apparent at this time, it is well accepted that pregnancy produces a state of nutritional, hormonal, circulatory, and emotional stress, the quantitative importance of any or all of which is yet to be determined. That these stresses during pregnancy do affect the constituents of serum has been demonstrated by recent studies which have determined the alterations of serum lipid and protein during the various stages of pregnancy and the postpartum period. 92-94 The relationship, if any, of these alterations to each other is probably quite complex since many of these changes appear to be in opposite directions. Thus, for example, beta lipoprotein rises while alpha lipoprotein decreases, albumin and gamma globulin decrease while alpha-1, alpha-2 and beta globulins increase as the pregnancy progresses. Some of these changes do not return to normal until 3 to 6 months after delivery. A change in the serum concentration of properdin during pregnancy would thus not be unexpected in view of the other alterations of serum constituents during pregnancy, although this decrease in properdin during pregnancy appears to occur in spite of the probable increase in levels of beta globulin during pregnancy.

In spite of a possible fall in gamma globulin during the latter part of pregnancy, there does not seem to be any decrease in the ability of pregnant females, both human and animal, to form antibodies against a number of antigens, examples of which are the normal levels of antibody produced against poliomyelitis virus, 95, 96 vaccinia virus,8, 20 typhoid bacteria,8 and ovalbumin.97 This apparently intact ability of pregnant women to produce specific antibodies tends to give added importance to the factors involved in nonspecific or natural immunity and, in such a situation, alterations in properdin concentration very likely play a significant role. Although in most instances in experimental infection, when properdin is lower than normal and decreased survival is observed, properdin would be expected to be the limiting factor, it is also conceivable that situations may arise where coms,

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plement could limit the extent of protection and in addition, where both complement and properdin could prove limiting. It must also be stated that in infectious diseases, pregnancy, and other states of decreased resistance, the exact finite limiting concentration of properdin has not been determined and may vary considerably depending upon the infecting organism to which the animal or human is exposed and upon its ability to produce specific antibody.

In general, however, the data presented in this paper add more evidence to support the concept of the essential role of the properdin system in natural immunity. The relationship which these changes in serum properdin during pregnancy have to many of the nutritional, hormonal, emotional, and other alterations produced by pregnancy warrant further investigation and could add to our understanding of the many factors which may be related to the properdin system and to natural resistance in general.

Summary

1. A review of the literature provides evidence that pregnancy produces a decrease in natural resistance to infections due a variety of bacteria, viruses, and protozoa and to infection due to coccidioides immitis.

2. Properdin concentrations were determined in the sera of 125 pregnant women

between the ages of 17 and 40. Statistical analysis revealed that the mean properdin concentrations during the first and second trimesters were definitely lower than that of normal white patients of the same age group and is possibly lower than normal during the third trimester. During the first, second and third trimesters, respectively, 38.7, 25, and 11.4 per cent of individual determinations were below the normal range.

3. The results of experimental investigations both in vitro and in vivo demonstrating the role of properdin in natural resistance to a variety of infectious diseases are compatible with the hypothesis that decreased natural immunity during pregnancy is at least partially due to a decreased serum properdin concentration. This possible causal relationship is given further support by the results of several investigations of the role of properidin in natural resistance to coccidioidomycosis.

4. The possible mechanisms by which properdin might be decreased during pregnancy are discussed.

We gratefully acknowledge the cooperation of Dr. Frank W. McKee, Director of Clinical Laboratories, in obtaining the sera and Drs. Daniel G. Morton and J. George Moore, Department of Obstetrics and Gynecology, for permission to study cases of patients in the Obstetrics Clinic.

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Pneumothorax, bilateral, spontaneous, complicating pregnancy

Case report

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SPONTANEOUS PNEUMOTHORAX is a term used to describe a pneumothorax that occurs suddenly in an otherwise apparently healthy person. It occurs chiefly among young men and quite often after external trauma but is not always related to physical activity.2 It is a relatively common condition in the general population but has not been reported frequently in pregnant women. In general, it is a benign condition and recovery is usually complete; however, there may be long periods of disability.2 The exact etiology of pneumothorax is not known; it is quite often related to a history of tuberculosis either in the present or a past episode and it is also known to occur from rupture of congenital cyst of the lung and from emphysematous blebs. We are reporting this case of spontaneous bilateral pneumothorax in the last trimester of pregnancy because of the paucity of reports of this condition complicating pregnancy.

The patient was a 26-year-old white woman, gravida ii, para i (twins). The last menstrual period was April 15, 1958, with an estimated date of confinement of Jan. 22, 1959. This patient was admitted to the William Beaumont

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Army Hospital on Nov. 22, 1958, with a chief complaint of dyspnea and chest pain of sudden onset. The patient had a history of two previous episodes of spontaneous pneumothorax on the left, the first episode being treated in 1955 at the Fitzsimons Army Hospital. At that time the patient was completely evaluated for pulmonary disease, but no etiological factor could be found and it was felt that the pneumothorax was due to spontaneous rupture of congenital blebs. In August, 1957, the patient had a repeat episode of spontaneous pneumothorax, this time of the right lung. She was treated by conventional methods in a civilian hospital. One day prior to admission to this hospital the patient had complaints of coughing and moderate dyspnea which were attributed to a chest cold. On the day of admission the patient experienced the sudden onset of inspiratory chest pain and dyspnea. She was admitted to this hospital with a diagnosis of spontaneous pneumothorax. The prenatal course up to this point had been completely uneventful. Past obstetrical history showed that she had been delivered of twins with her first pregnancy, which had been complicated by a kidney infection and "impending pre-eclampsia." On this admission to the hospital the patient was noted to be in acute respiratory distress, but she was alert and cooperative. The chest examination revealed splinting of the left hemithorax and hyperresonance of the upper portion of the left chest with absent breath sounds. The lower portion had bronchial type sounds. The right lung was normal. The abdomen was enlarged to a size compatible with a 31 weeks' gestation. The fetus was

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in a cephalic presentation and the heart sounds were normal. Initial roentgenography revealed pneumothorax of the left lung involving 60 to 70 per cent of the entire lung volume. The right lung and mediastinal structures were reported as normal. On Nov. 23, 1958, under local anesthesia, a left thoracotomy with closed drainage was established. The lung completely re-expanded and the tube was removed in 3 days. Concomitant treatment was bed rest, antibiotics, and minimal sedation and analgesia as needed. The patient was discharged in 6 days with no evidence of pneumothorax. The day following discharge she was readmitted to this hospital with chest pain on the right side, shortness of breath, and cyanosis. X-ray examination of the chest at this time revealed 50 to 60 per cent pneumothorax on the right and 10 to 15 per cent on the left (Fig. 1). A bilateral thoracotomy with closed drainage was established. The day following the insertion of the thoracotomy tube, the left lung showed good expansion but the right lung remained collapsed to 35 per cent of its original capacity. During the patient's hospital stay on bed rest, sedation, and antibiotics, serial films were taken and by Dec. 2, 1958, both lungs were well expanded. During the hospital stay the patient had frequent episodes of acute chest pain, cyanosis, and dyspnea, which were relieved by nasal oxygen, readjustment of thoracotomy tube, and sedation. Uterine irritability was marked with irregular episodes of strong contractions believed to be Braxton Hicks in nature. On Dec. 4, 1958, shortly after removal of the right thoracotomy tube, the patient again developed a



Fig. 1.



Fig. 2.

severe pain in the left side of the chest with dyspnea and cyanosis. Chest films revealed a moderate tension pneumothorax on the right side with a definite shift of the heart and mediastinum to the left (Fig. 2). The right lung was collapsed 35 per cent of its original volume and treatment was started immediately. The patient was hospitalized until Jan. 8, 1959, and during this stay serial films showed the lungs to reexpand to their original volume of 90 per cent. On Jan. 5, 1959, the patient went into spontaneous labor. Continuous caudal block was selected for analgesia as well as anesthesia, and the patient was delivered over a midline episiotomy with low forceps of a viable female infant, weighing 5 pounds, 14 ounces. The entire duration of labor was 3 hours, 26 minutes, and the patient and baby tolerated the labor and delivery well. The postpartum course was uneventful. Eight days after delivery the right lung was completely re-expanded without noticeable changes of the left lung. On Jan. 21, 1959, breathing exercises were started and on Jan. 22, 1959, under general anesthesia, a right thoracotomy was performed with resection of large apical pulmonary bullae and oversewing of multiple small pulmonary blebs. A chest tube was left in for 7 days and recovery was uneventful. At a later date the patient was readmitted to the hospital where a left thoracotomy was performed on March 3, 1959, with excision of the apical blebs. Recovery was complete and the patient was finally discharged on March 11, 1959. On follow-up studies the patient has had no other episodes of pneumothorax.

Comment

The diagnosis of pneumothorax is relatively easy and should be suspected in an acute onset of chest pain which is associated with dyspnea and cyanosis. The physical examination will show absence of breath sounds in the affected area; percussion elicits hyperresonance or tympany, and x-rays of the chest will establish the diagnosis.2 The treatment of pneumothorax ranges from conservatism in the very mild cases to thoracotomy in the chronic recurrent severe cases. The average mild case can be satisfactorily treated with conservatism.1 The usual case of pneumothorax is treated with closed drainage by means of an intercostal catheter, and if re-expansion fails to occur properly a bronchoscopy may help by clearing the bronchial secretions which may have prevented re-expansion. Operation is the treatment of choice in the chronic recurring type of spontaneous pneumothorax and also in the acute type that does not respond to conservative treatment. Other methods of treatment that have been suggested include the instillation of chemicals into the chest to produce pleuritis, causing adhesion of the visceral pleura to the parietal pleura. The surgical procedure that will be necessary is determined at the time of the thoracotomy by the pathological condition that is encountered. Some of the complications that can occur with spontaneous pneumothorax are tension pneumothorax, bilateral collapse of the lung, hemopneumothorax, and recurrent and chronic pneumothorax.2, 3 The case reported was that of a bilateral chronic recurring spontaneous pneumothorax in a woman who was approximately 31 weeks gravid. The potential problem in this case was that of fetal distress due to the anoxia which this patient was exhibiting. It was felt that the same principles of treatment should be followed in this patient as in a nonpregnant patient. It was also felt that termination of the pregnancy was not indicated or desirable at this time because of the length of the gestation. At this point several problems were evident. How should pregnancy be terminated when the patient reached term? What

type of anesthesia was best suited for delivery? Vaginal delivery was indicated obstetrically and would obviate the possible added respiratory embarrassment of an abdominal procedure. Continuous caudal analgesia and anesthesia were selected for relief of pain and apprehension, and to prevent the desire or urge to "bear down" in the second stage, which might result in another episode of pneumothorax. This patient continued with the pregnancy until approximately 2 weeks before term when she went into spontaneous labor. At the beginning of labor the membranes were ruptured and a polyvinyl catheter was placed in the caudal canal and analgesia and anesthesia were effected with multiple injections of 1 per cent Xylocaine. The patient and baby tolerated the labor and delivery well. The patient had no straining or pushing during the second stage of labor and the labor was terminated by low forceps delivery of a normal child. We feel that the treatment of spontaneous pneumothorax in the pregnant patient should follow the same principles as that in the nonpregnant patient. The concern of the obstetrician should be that of labor and delivery, and, if the patient can be treated with continuous caudal anesthesia to prevent any pain or pushing and increased abdominal tension, we feel that she can safely be delivered vaginally.

Summary

- 1. A case of pneumothorax complicating pregnancy is reported.
- 2. We feel the same principles of treatment as for the nonpregnant should be followed.
- 3. Vaginal delivery is best if there are no obstetric reasons for abdominal delivery.
- 4. Continuous caudal analgesia and anesthesia are indicated.

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Maternal isosensitization to the red cell antigen U

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While studying a patient who died of a blood transfusion reaction, Wiener and associates found an immune isoantibody of high titer and avidity. This antibody agglutinated the red cells of 421 of 425 Negroes tested and of all of the 690 white patients studied. The antigen present in the red cells that were agglutinated by this previously unknown antibody was called "U" to avoid confusion with the other blood groups and because it appeared to be universally present in all patients originally tested.

Greenwalt and Sanger and their associates^{2, 3} showed that U-negative individuals lack both S and s antigens in the red cells and that there is an association between U and the MNSs system. They proposed that a third allele S^u is located at the Ss locus and that only those individuals who are homozygous for this allele are U negative. The antibody, anti-U, was found to behave as if it were an inseparable combination of anti-S plus anti-s.

The literature contains references to only four examples of anti-U, 1, 2, 4, 5 all of which were associated with problems in transfusion. In addition, there have been at least 2 unpublished cases of the newborn due to this antibody. The purpose of this report is to describe a patient sensitized to the U antigen who was followed through 2 pregnancies, one of which resulted in hemolytic disease of the newborn.

From the Department of Obstetrics and Gynecology, University of Washington School of Medicine, and the King County Hospital.

Case report

Present illness. M. K., a 26-year-old Negro woman, gravida vi, para v, was admitted in labor to the King County Hospital on Aug. 5, 1959. The last menstrual period had occurred on Oct. 29, 1958, and the estimated date of confinement was Aug. 6, 1959. She had been followed in the Obstetric Clinic since May 25, and the prenatal course was entirely normal. She was known to be sensitized to the U factor. Repeated blood studies during this pregnancy revealed anti-U antibodies of 1:32 titer that remained unchanged during the prenatal period. On admittance she complained of regular, intermittent, painful lower abdominal cramps and denied rupture of membranes or vaginal bleeding.

Past history. The patient had had childhood measles, mumps, and diphtheria. She had been healthy all her life and had had no operations or accidents. She denied ever having received a blood transfusion. She had had 5 full-term normal intrauterine gestations. All children were living and well and none had ever developed jaundice or required blood transfusions. The first 4 gestations resulted from Father A; the fifth gestation, Father B; the sixth gestation, Father C. The first infant was a 6 pound girl delivered in May, 1950, by low forceps under spinal anesthesia. The second infant was a 5 pound, 9 ounce boy delivered in January, 1952, also by low forceps extraction. The third and fourth infants were a 6 pound, 2 ounce boy and a 6 pound, 4 ounce girl, respectively, born by normal spontaneous deliveries in February, 1953, and July, 1955. During the fifth pregnancy, it was discovered on routine prenatal blood studies that the patient was Group B, Rh positive (cDE/cDe) with a positive indirect Coombs test. The antibodies present were identified as anti-U; the patient was found to be U negative

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While studying a patient who died of a blood transfusion reaction, Wiener and associates found an immune isoantibody of high titer and avidity. This antibody agglutinated the red cells of 421 of 425 Negroes tested and of all of the 690 white patients studied. The antigen present in the red cells that were agglutinated by this previously unknown antibody was called "U" to avoid confusion with the other blood groups and because it appeared to be universally present in all patients originally tested.

Greenwalt and Sanger and their associates^{2, 3} showed that U-negative individuals lack both S and s antigens in the red cells and that there is an association between U and the MNSs system. They proposed that a third allele S^u is located at the Ss locus and that only those individuals who are homozygous for this allele are U negative. The antibody, anti-U, was found to behave as if it were an inseparable combination of anti-S plus anti-s.

The literature contains references to only four examples of anti-U,^{1, 2, 4, 5} all of which were associated with problems in transfusion. In addition, there have been at least 2 unpublished cases⁶ of hemolytic disease of the newborn due to this antibody. The purpose of this report is to describe a patient sensitized to the U antigen who was followed through 2 pregnancies, one of which resulted in hemolytic disease of the newborn.

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Case report

Present illness. M. K., a 26-year-old Negro woman, gravida vi, para v, was admitted in labor to the King County Hospital on Aug. 5, 1959. The last menstrual period had occurred on Oct. 29, 1958, and the estimated date of confinement was Aug. 6, 1959. She had been followed in the Obstetric Clinic since May 25, and the prenatal course was entirely normal. She was known to be sensitized to the U factor. Repeated blood studies during this pregnancy revealed anti-U antibodies of 1:32 titer that remained unchanged during the prenatal period. On admittance she complained of regular, intermittent, painful lower abdominal cramps and denied rupture of membranes or vaginal bleeding.

Past history. The patient had had childhood measles, mumps, and diphtheria. She had been healthy all her life and had had no operations or accidents. She denied ever having received a blood transfusion. She had had 5 full-term normal intrauterine gestations. All children were living and well and none had ever developed jaundice or required blood transfusions. The first 4 gestations resulted from Father A; the fifth gestation, Father B; the sixth gestation, Father C. The first infant was a 6 pound girl delivered in May, 1950, by low forceps under spinal anesthesia. The second infant was a 5 pound, 9 ounce boy delivered in January, 1952, also by low forceps extraction. The third and fourth infants were a 6 pound, 2 ounce boy and a 6 pound, 4 ounce girl, respectively, born by normal spontaneous deliveries in February, 1953, and July, 1955. During the fifth pregnancy, it was discovered on routine prenatal blood studies that the patient was Group B, Rh positive (cDE/cDe) with a positive indirect Coombs test. The antibodies present were identified as anti-U; the patient was found to be U negative

and her genotype was presumed to be SuSu. The antibody titer was 1:16. During the thirty ninth week of pregnancy, U-negative blood was obtained from Dr. Greenwalt of Milwaukee. Labor was induced at term on Jan. 2, 1957, by intravenous infusion of 10 units of Pitocin in 1,000 c.c. of 5 per cent dextrose in water. After a labor of 3 hours and 10 minutes, a 6 pound, 2 ounce male infant was delivered spontaneously. The infant was Group O, Rh positive, U negative. Cord blood hemoglobin, reticulocyte count, and smears were normal. The direct Coombs test on the cord blood was negative, and the child's serum was demonstrated to contain anti-U antibodies. The infant developed normally with an uncomplicated neonatal course. The mother had a normal puerperium. She was not seen again until the twentieth week of the sixth pregnancy.

Physical examination. When the patient was admitted during the sixth pregnancy, the temperature was 98.7° F., pulse 82 per minute, blood pressure 120/70, and respirations 20. She was a well-developed, well-nourished Negro woman complaining of intermittent lower abdominal cramps. Examination of the eyes, ears, nose, throat, neck, and breasts revealed no abnormalities. The lungs were clear to percussion and auscultation. The heart was not enlarged, the heart sounds were normal, and there was a normal sinus rhythm. Examination of the abdomen revealed a uterus enlarged to 32 cm. above the symphysis pubis, soft, cystic, nontender with intermittent contractions every 5 minutes of moderate to strong intensity lasting 60 seconds. The fetus was in the left occipitotransverse position and the fetal heart tones were regular and strong in the left lower quadrant at 140 per minute. Rectal examination on admission revealed the cervix to be 2 cm. dilated, 60 per cent effaced; the presenting part was at Station plus-2 and the membranes were intact.

Laboratory data on admission. The hematocrit determination was 36 per cent and the leukocyte count was 9,200 with a normal differential. Urinalysis revealed normal findings. The chest x-ray findings were normal and the VDRL was negative. On the third day after delivery, the hematocrit determination was 37 per cent and the leukocyte count was 8,700 with normal differential.

Hospital course. The patient was admitted in early labor on Aug. 5, 1959. U-negative blood from a Seattle donor was obtained for use if

necessary. The labor progressed normally and the contractions became strong and regular every 3 minutes, lasting 45 to 60 seconds. After 1 hour and 50 minutes, the cervix was fully dilated and effaced and the presenting part was at Station plus-2. Under pudendal block anesthesia, a normal spontaneous delivery of a 6 pound, 15 ounce male infant was accomplished over an intact perineum 14 minutes after the beginning of the second stage of labor. The infant cried and breathed immediately after birth and appeared entirely normal. The third stage of labor lasted 19 minutes and the placenta was delivered by modified Credé maneuver. The placenta weighed 475 grams and measured 15.5 by 18.5 by 2 cm. The placenta was intact and appeared grossly normal. The fourth stage of labor was normal. After 5 days of a normal puerperal course, the patient was discharged home to return to the Postpartum Clinic.

The infant was of blood Group A, Rh positive, U positive, with a positive direct Coombs test. Cord blood at the time of birth showed a hemoglobin level of 20.5 Gm. per cent, a reticulocyte count of 4.2 per cent, and a bilirubin level of 1.9 mg. per cent. Smear of the cord blood was within normal limits. Twentyfour hours after birth the hemoglobin level was 21 Gm. per cent, reticulocyte count 4.8 per cent, and bilirubin level 3.7 mg. per cent. Seventy-two hours after birth the bilirubin level was 5.4 mg. per cent. There was no further rise of the bilirubin. Physical examination on discharge revealed an entirely normal infant. Careful histologic study of the placenta disclosed few amniotic cysts but no other abnormalities or traits of erythroblastosis fetalis.

Comment

With the continuous discovery of new blood group systems, new antigens, and new antibodies, the understanding of the problems of fetal maternal sensitization has become quite complex for the average obstetrician. This knowledge is very valuable in the prognosis, diagnosis, and treatment of the complications resulting from fetal-maternal incompatibilities. Specialized laboratories should determine the blood grouping of every pregnant woman and the presence or absence of maternal immune antibodies during each subsequent pregnancy.

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The case presented illustrates this point. The patient was seen by us for the first time during the fifth pregnancy. Even though we knew that she was Rh positive, a sample of blood was obtained. The patient's blood was typed, and an indirect Coombs test revealed immune antibodies which were identified as being anti-U with a titer of 1:16. The patient's blood was found to be U negative, probable genotype SuSu. The red cells lacked both S and s antigens as shown by agglutination and absorption tests with anti-S, anti-s, and anti-U antibodies. The mother and the fetus were in potential jeopardy because no compatible (U-negative) blood could be found in Seattle. Had this patient needed blood because of a complication of pregnancy or for any other reason, we would have been unable to give it to her. Also, the possibility of hemolytic disease of the infant was real. The alleged father (Father B) was not available for typing and on presumptive basis would be U positive and most likely would be lacking the gene Su. The infant would then have either the antigen S or s in his red cells and would have been susceptible to the mother's anti-U (S + s) antibodies. If exchange transfusion of the newborn infant were needed, the mother could have been used as donor even though this would not have been ideal in view of the incompatibility between her plasma and the infant's red cells.

Following delivery, this infant was found to be U negative (S^uS^u). While the antibodies were present in his plasma, his red cells remained unaltered, and a normal neonatal course followed. The maternal anti-U antibody titer remained unchanged during the puerperium. The mother had been sensitized by previous U-positive fetuses as shown by family studies and had never received blood in any form. Fetal s antigen was the sensitizing factor as suggested by Table I and by more complete evaluation of the blood group systems found in family kin.⁷

Wiener and associates⁸ pointed out that U is most likely inherited as a simple Mende-

Table I. Blood groups in family of M. K.

Mother	B, U-negative (NS ^u NS ^u), Rh+
Father A	B, U-positive (MsNs), Rh+
First child	O, U-positive (NsNSu), Rh+
Second child	B, U-positive (MsNS"), Rh+
Third child	B, U-positive (MsNS ^u), Rh+
Fourth child	O, U-positive (NsNSu), Rh+
Father B	Unknown
Fifth child	O, U-negative (NS"NS"), Rh+
Father C	Unknown
Sixth child	A, U-positive (MsNSu), Rh+

lian dominant by a pair of allelic genes U and u where gene U determines the presence of the factor and gene u its absence. Therefore, U-negative individuals would be homozygous uu, and U-positive patients would be homozygous UU or heterozygous Uu. Following the discovery by Greenwalt and Sanger and their co-workers2, 3 that U-negative individuals lack both S and s antigens and that anti-U antibodies behave as an inseparable combination of anti-S and anti-s antibodies, it would seem reasonable to consider u as an allele at the Ss locus and to use Su as its symbol. According to this hypothesis, U-negative individuals are SuSu homozygous and Upositive persons are S or s homozygous (SS or ss) or heterozygous (SuS, Sus, Ss). The gene frequency of Su in the Negro population is approximately 0.0529.9 These authors found the S^uS^u genotype in only 4 of 1,429 Negroes tested, while Wiener⁸ found it in 12 of 977 Negroes studied. In Caucasians the existence of Su(u) antigen or of red cells without both S or s antigens is extremely rare or is lacking. Wiener and associates⁸ studied 1,100 Caucasians and found all of them to be U-positive, and Greenwalt and co-workers2 tested 1,000 Caucasians and found no red cells where both S and s antigens were absent.

In view of the cases of isosensitization reported, of which one was fatal, there is no question of the existence of an antibody that reacts both with S and s antigens. We still do not know, however, whether individuals are U-negative because of deletion at the Ss locus or because of the presence

of a new antigen such as Su(u). The answer to this question will be obvious if and when anti-Su antibodies are found. To clarify this point, Sanger and associates3 injected 14 white volunteers with 2 c.c. of SuSu blood but failed to produce sensitization and anti Su antibodies. Regardless whether there is a Su antigen or simply a deletion of Ss antigens, the fact remains that these individuals can become sensitized by U-positive red cells due either to pregnancy or to the administration of blood and therefore hemolytic disease of the newborn or blood transfusion reactions may result.

Because the patient was aware of her problem she returned to see us during the twentieth week of her sixth pregnancy. She stated that she had conceived from another man whom we called Father C. Anti-Ss antibodies (anti-U) were still present in the serum and the titer was 1:32. This increase in titer as compared to the one found during the previous pregnancy (1:16) was probably not significant. Father C was not available for typing.

The prenatal course of this pregnancy was uncomplicated, and after a normal spontaneous labor a normal male infant was born. As we expected, this infant was U positive (s+) and his red cells were coated with Ss antibodies as shown by the direct Coombs test. No hemolytic disease developed, however, and even though the direct Coombs test remained positive at least until the eighth week, no anemia or hyperbilirubinemia was detected. The infant developed normally and, like his brothers and sisters, is healthy and shows no signs or symptoms of hemolytic disease.

The antibody titer of the mother remained unchanged through the puerperium as had happened after the fifth pregnancy. These antibodies were of the incomplete or univalent variety.

This case illustrates maternal sensitization to fetal U factor and the potential development of hemolytic disease of the newborn due to anti-U (S + s) antibodies. The mild nature of the present case does not necessarily imply that this given antibody will not cause in another instance severe or fatal red cell destruction.

Summary

- 1. A case of sensitization of a U-negative mother by U-positive fetuses has been presented.
- 2. This patient was followed through two pregnancies without significant change in the anti-U antibody titer.
- 3. One pregnancy (the fifth) resulted in the birth of a healthy U-negative baby with a positive indirect Coombs test.
- 4. The other pregnancy (the sixth) resulted in the birth of a U-positive infant. Even though the laboratory findings characteristic of hemolytic disease of the newborn were present, no clinical disease was noted.
- 5. In addition to ABO and Rh typing, every pregnant woman should have an indirect Coombs test with each pregnancy if maternal sensitization is to be detected.

We wish to express our thanks to Dr. Eloise Giblett, Associate Director of the King County Central Blood Bank, and to her associates, who assisted us in the study of this case.

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Fetomaternal ABO incompatibility: intravascular hemolysis, fetal hemoglobinemia, and fibrinogenopenia in maternal circulation

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ACQUIRED fibrinogenopenia occurring in pregnancy is an established clinical entity, but its etiology is unsettled. Schneider's concept13, 15 suggests that tissue thromboplastins derived from decidual or placental sources may enter the maternal blood stream and initiate intravascular coagulation-which consumes the maternal fibrinogen by "defibrination." Other investigators7 believe a cytofibrinokinase located in placenta and uterus may activate the maternal fibrinolytic system. Fibrinolysin when converted from its inactive form in plasma (profibrinolysin) may attack both fibrin and fibrinogen as protein substrates and induce hemorrhage with fibrinogenopenia. Both mechanisms may operate simultaneously, so a precise statement as to which event is dominant is not yet forthcoming.17

In this paper sequences in a case study of ABO heterospecific pregnancy provide another approach to the pathogenesis of maternal fibrinogenopenia.

Materials and methods

Coagulation studies. Venous clotting time was measured in silicone-coated tubes (normal, 25 to 45 minutes) and the one-stage prothrombin by Quick's method (normal,

12 to 15 seconds, 70 to 100 per cent). The plasma fibrinogen titer was assayed by the procedure of Bowman and Yelito (normal, 1:100 to 1:400).²

Fibrinolytic activity was estimated against fibrin substrates derived from (a) normal plasma, and (b) a standard fibrinogen solution. In (a) plasma was obtained by centrifuging whole blood, drawn from the patient and a normal individual into 19 per cent citrate (4.9 ml. blood per 0.1 ml. citrate). A test mixture of 0.5 ml. normal plasma and 0.5 ml. of the patient's plasma and a control mixture of 0.5 ml. normal plasma and 0.5 ml. imidazole saline buffer were mixed and coagulated with 0.1 ml. (10 units) human thrombin (Fibrindex, Ortho Pharmaceutical Corporation). In (b) a 1 per cent solution of Armour's bovine fibrinogen was prepared in imidazole saline buffer, and human thrombin was dissolved in 3.5 ml. imidazole saline buffer and 0.5 ml. glycerine so that 0.2 ml. of homogenous glycerinized solution contained 4 units of thrombin. The test mixture consisted of 0.4 ml. of the patient's plasma and 0.2 ml. fibringen and the control mixture of 0.4 ml. normal plasma and 0.2 ml. fibrinogen. Both systems were mixed and coagulated by adding 0.2 ml. of thrombin solution.

Fibrinolysin assays in both (a) and (b) were transferred at once to a 37° C. water bath and were examined at one minute intervals for 30 minutes for beginning clot

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lysis as evidenced by separation of the fibrin clot from the sides of the tube. Incubation was continued at 37° C. for 24 hours to complete the observation for clot lysis.

Plasma hemoglobin; estimation of fetal hemoglobin in maternal plasma. The hemoglobin content of maternal plasma samples was determined by the method of Crosby and Furth.⁴ A mean value for normal subjects studied in these laboratories is 1.5 ± 1.0 mg. per cent (range, 0 to 4 mg. per cent), with this technique.

From the multiple procedures necessary in this investigation only a small amount of maternal plasma was available to estimate the variety of hemoglobinemia. For such analysis, the plasma proteins were separated from the maternal specimen by ultracentrifugation, and the sample then dialyzed and its hemoglobin content concentrated.* The concentrate was divided into two aliquots. One half was reacted against distilled water as a control, and the other one half was treated with N/12 sodium hydroxide and its alkali-resistant (fetal) hemoglobin component measured by the method of Singer.¹⁶

Immunohematologic procedures. The red cells of the mother and infant were examined for their ABO and Rh blood groups by test tube methods. Maternal red cells were reacted in the direct tube antiglobulin test (Coombs) and studied for the intraerythrocyte defect of paroxysmal nocturnal hemoglobinuria by both the Ham acidserum method and the Crosby thrombin procedure.5 The maternal serum was treated for detection of any biphasic hemolysin in the Donath-Landsteiner reaction and also combined against a standard Group O red cell test panel containing all representative blood group antigens in a search for extraneous antibodies other than anti-A or anti-B.

The nature of the anti-B agglutinin in the maternal serum was characterized with serial twofold dilutions of this antiserum in

*The physical separation and procedure were performed by the Division of Hematology, Jefferson Medical College, Philadelphia. saline, and a second set of identical dilutions made in saline after neutralization with purified B substance (Merck Sharp & Dohme), following the partial neutralization titration procedure of Witebsky.¹⁸ The anti-B isoantibody was neutralized by means of the proportion of 3 parts of serum to 1 part B substance. The 0.1 ml. dilutions of the maternal serum were added to an equal volume of 2 per cent suspension of fresh Group B red cells. The resultant mixtures were incubated for 60 minutes and incubation temperature varied from 20 to 24° C. The tubes were centrifuged and agglutination reactions read macroscopically. A third set of the same saline dilutions of the maternal serum neutralized with B Substance was combined with 2 per cent saline suspensions of Group B red cells, incubated similarly, and an indirect anti-globulin test (Coombs) completed.

Results

Case presentation. R. E., a 27-year-old white housewife, gravida iv, para iii, entered the Harrisburg Hospital, Sept. 20, 1958, at the fortieth week of gestation. At bedtime antedating admission the patient had taken 2 ounces of castor oil for self-induction. At 3:45 A.M. on the morning of admission, she was found by her husband in a semiconscious state on the bathroom floor, exhibiting uncontrolled diarrhea and violent and rapid uterine contractions. She was transported at once to the hospital by ambulance and when examined was found to be pallid with a rapid thready pulse, blood pressure 78/40, and in a state of shock with cold moist skin. After precipitous labor of less than one hour, a 7 pound, 12 ounce female infant was delivered. The placenta was inspected with no evidence found indicating premature separation or disturbed gross anatomy.

Profuse postpartum bleeding followed despite fundal massage and an intravenous Pitocin infusion. The uterus was small and well-contracted, and the cervix was intact. The vaginal blood appeared liquid, a fibrinogen titer disclosed afibrinogenemia, and venous blood was incoagulable. "Plasma" was salvaged from two venous specimens trawn for determining venous clotting time and fibrinogen titer, and it was used in the fibrinolysin assays and plasma hemo-

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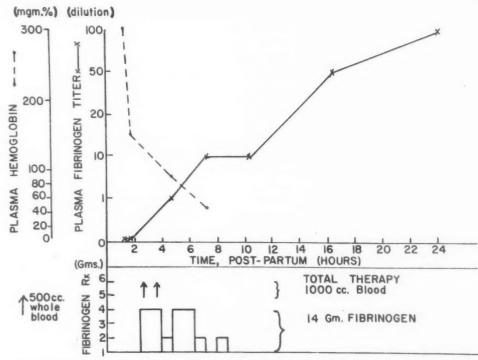


Fig. 1. Determinations of plasma hemoglobin and fibrinogen titers with replacement therapy for fibrinogenopenia, Patient R. E.

globin measurements described later. These samples taken before the patient had received either fibrinogen or blood transfusion therapy were noted to be bright pink in color. The cause for this intravascular hemolysis and hemoglobinemia within the maternal plasma was not immediately apparent, but additional specimens were collected to measure plasma hemoglobin. The acquired hemorrhagic disease was treated with 1,000 ml. whole blood and 14 Gm. of intravenous fibrinogen according to a scheme subsequently shown and discussed (Fig. 1).

The 24 hour output post partum was only 300 ml. of dark brown-colored urine. Its specific gravity was 1.010 in a noncatheterized specimen, and there was 4 plus proteinuria, partially due to some contamination of the specimen with vaginal blood. Oliguria, with outputs from 150 to 350 ml. of urine volume, persisted in the first 4 days after delivery. Because of the hemoglobinemia, the patient was managed conservatively for a lower nephron nephrosis. Hyposthenuria remained at 72 hours post partum together with presence of rare red cells and occasionally granular casts in the microscopic urinary sediment. At this time a mild lower

nephron syndrome was evidenced in the blood chemistry values. The blood urea nitrogen level was 51 mg. per cent, creatinine 4.2 mg. per cent, CO₂ combining power 50 vol. per cent, serum potassium 5.0 mEq. per liter, sodium 138 mEq. per liter, chlorides 101 mEq. per liter, and calcium 9.3 mg. per cent. A diuretic phase followed on the tenth day post partum, and the azotemia then cleared by the time of discharge on the twentieth day. At this interim the only measured abnormality in renal function was hyposthenuria, with a urinary specific gravity of 1.010.

The newborn infant was a 7 pound, 12 ounce lethargic female in respiratory distress. There were many inspiratory wheezes and rhonchi heard in auscultation of the chest, and chest roentgenogram disclosed a small area of segmental atelectasis in the left upper lobe. At 20 hours in the neonatal period, the infant's dyspnea increased. She exhibited inspiratory retraction of the ribs and suprasternal notch, together with repeated clonic spasms of all extremities. Atraumatic lumbar puncture disclosed 15,000 erythrocytes per cubic millimeter of cerebrospinal fluid, with elevation of the protein

Table I. Measurements of coagulation in maternal blood (R. E.)

				Fibrinolysin of fibrin	Total	
Time (post partum)	Venous clotting time (minutes)	Prothrom- bin (%)	Fibrinogen titer (dilution)	Normal plasma	Standard fibrinegen solution	amounts intravenous fibrinogen
1 hour, 34 minutes	Incoagulable		0	0 Lysis	0 Lysis	None
1 hour, 45 minutes	Incoagulable	-	0	0 Lysis	0 Lysis	None
7 hours, 15 minutes	21	35	1:10	_	_	12 Gm.
24 hours	28	100	1:100		-	14 Gm.

content to 407 mg. per cent. The child died 33 hours post partum in spite of supportive management. A single examination of the infant's peripheral blood showed a hemoglobin level of 16 Gm. per cent and a hematocrit value of 53 vol. per cent.

At necropsy examination, focal pulmonary atelectasis and congestion of both lungs were found. The bronchi contained yellowish mucoid exudate. There was an area of intraventricular hemorrhage present in the left lateral ventricle, and petechial hemorrhages were scattered throughout the brain stem. Both adrenal glands were replaced by hemorrhage. These were the only hemorrhagic lesions as determined by a complete autopsy.

Blood coagulation data. Some serial measurements of coagulation made upon maternal blood are presented in Table I.

In the early postpartum period the profound deficit in circulating maternal fibrinogen was clearly demonstrated by incoagulable venous blood and a fibrinogen titer of 0. The limited assays for fibrinolysins disclosed no evidence of enhanced fibrinolytic activity within the maternal plasma. In the controls for this assay, no lysis was found in either system at the 30 minute observation period and minimal lysis was seen after 24 hours. Following administration of 12 Gm., of intravenous fibrinogen, a prolonged one-stage prothrombin time and a diminished fibrinogen titer of 1:10 indicated continuing fibrinogenopenia, although venous clotting time had returned to a normal level. In 24 hours, all measurements of the patient's coagulation system were normal and were unaltered thereafter.

Treatment of fibrinogenopenia and hemoglobinemia. Serial estimations of the hemoglobin detected in maternal plasma together with the values of the fibrinogen titer and the substitution therapy involving intravenous fibrinogen and whole blood transfusions are shown in Fig. 1. The ordinates express the plasma hemoglobin in milligrams per cent, plasma fibrinogen titer as its dilution, and the amounts of intravenous fibrinogen therapy in grams. The abscissa represents the postpartum time in hours.

Hemoglobinemia in maternal plasma was determined as 300 mg. per cent and later as 150 mg. per cent in two samples taken before administration of any blood or intravenous fibrinogen. The plasma gradually lost its pink appearance and became dark brown and then amber in color as the amounts of hemoglobin declined to a low value of 46 mg. per cent in the last analysis made.

Even following the use of 6 Gm. of fibrinogen and 1,000 ml. whole blood, the fibrinogen titer of 0 was elevated only to a 1:1 dilution at 4 hours and 45 minutes after delivery. With this criteria for the effective circulating fibrinogen remaining at hemorrhagic levels, an additional 6 Gm. of fibrinogen was infused. At 7 hours and 15 minutes post partum, since the fibrinogen titer still was only 1:10 and soft, abnormal fibrin clots formed in the first two dilutions in this procedure, an additional 2 Gm. of fibrinogen was given. Without further transfusions of blood or fibrinogen, the titer reverted to a normal level of 1:100 at 24 hours' time.

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lyzed fetal and not maternal red cells.

Immunohematologic investigation. The red cells of the patient, R. E., were determined as being Group O, (Rh₀)D-positive. The direct tube antiglobulin test on these cells was negative and in the Ham acid-serum test no lysis of the patient's red cells occurred in her own or normal compatible serum at pH 6.8. Thrombin induced no hemolysis of the patient's erythrocytes by the Crosby procedure, so that the defect of paroxysmal nocturnal hemoglobinuria did not exist. The patient's postpartum serum

disclosed no isohemolysins or abnormal isoagglutinins against the Group O reference cell panel. There was no indication of autohemolysin or autoagglutinin in procedures involving autogenous red cells. No biphasic hemolysin of the Donath-Landsteiner variety was found which excluded that immunologic mechanism which produces "cold" hemoglobinemia with hemoglobinuria. The red cells of the fetus were reacted only for their blood group antigens which were Group B, $(Rh_0)D$ -positive.

Since fetomaternal incompatibility was established in a Group O mother who was delivered of a Group B infant, the anti-B agglutinin in postpartum maternal serum samples was examined. Two serums were available for this study, one obtained 6 hours post partum and another drawn 6 weeks post partum, and the results of this characterization are illustrated in Table II.

The complete antibody component, or agglutinin, in both maternal serums is contrasted in the first column in Table II. A titer of saline agglutinins of 1:4, lower than usual levels, was seen in the 6 hour specimen. In the 6 weeks' sample, the titer of this isoantibody had increased significantly to a level of 1:2,048. The 1:2 and the 1:4 dilutions of this antiserum contained an

Table II. Characterization of anti-B antibodies (R. E.)

	0.1 ml. of 2 per cent red cell suspensions							
0.1 ml. dilutions of serum (R. E.) (saline)	B cells serum not neutralized		B cells serum neutralized 3 serum: 1 B substance		B cells serum neutralized 3 serum: 1 B substance (Coombs)			
	No. 1*	No. 2*	No. 1	No. 2	No. 1	No. 2		
1:2	+	+++ (Hem. ++)	±	++	±	+++		
1:4	+	++++ (Hem. +)	±	++	_	++-		
1:8	±	++++		++	-	+++		
1:16	_	++++	_	++	_	+++		
1:32	_	+++	-	+	-	+++		
1:64		++ (+)	400	+	-	++ (+)		
1:128	stade	++	_	(+)	-	++ (+)		
1:256	-	++	series.	-	_	++ (+)		
1:512	time.	++	-	-	-	++		
1:1,024	_	+	-	control (Control (Con	eler	++		
1:2,048	_	(+)	_	-	_	+ (+)		
1:4,096	_	<u>+</u>	-		-	+		
1:8,192	_		-		-	(+)		
Diluent	-	-		_		_		

^{*}No. 1 serum, 6 hours post partum; No. 2 serum, 6 weeks post partum.

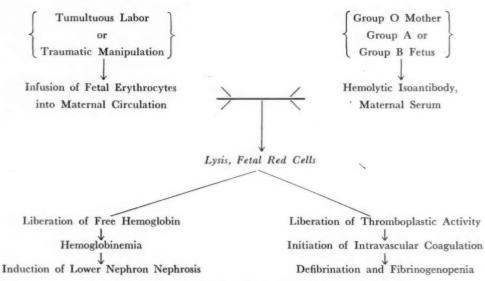


Fig. 2. Hypothetical dynamics of maternal fibrinogenopenia.

anti-B hemolysin as well as an agglutinin.

In the middle column in Table II, the ability of B substance to neutralize the anti-B isoagglutinin in maternal serum specimens is shown. In serum No. 1 (6 hours) there is complete neutralization of this weak antibody by B substance. In serum No. 2, the isohemagglutinin is partially neutralized from its previous titer of 1:2,048 to a titer of 1:128. In the third column of this table, the titration scores for the indirect antiglobulin portion of this experiment are listed as performed upon both neutralized maternal serums. With the addition of Coombs serum, only the 6 weeks post partum specimen exhibits a maximal increase in both titer and avidity from the agglutination readings in the middle column, in which the similar test mixtures lacked antiglobulin serum. The partial neutralization titer of 1:8,192 found in this maternal serum sample is indicative of an "immune-type" anti-B isoantibody.

Comment

Initially, the mechanism responsible for acquired fibrinogenopenia in this case was not obvious. In the emergency treatment of the resultant hemorrhagic disease, there was insufficient time to secure and determine more sensitive assays for fibrinolytic activity, as the Astrup fibrin plate method.¹ In the crude procedures performed upon fresh specimens, however, there was no evidence of any increase in fibrinolytic activity in the maternal plasma. The assumption seemed plausible that the pathogenesis of this patient's fibrinogenopenia evolved from the entrance of some thromboplastic material into the maternal blood rather than from intense activation of maternal fibrinolytic enzymes.

The source for hemoglobinemia in the maternal plasma was first assumed due to intravascular hemolysis of maternal red cells from an unexplained agent. Prompt study of the maternal red cells and serum disclosed no intrinsic red cell defect and no unusual blood group antibodies other than those of the ABO system. Lysis of sufficient red cells had occurred within the maternal circulation to liberate a product from erythrocyte destruction which induced temporary but definite lower nephron syndrome in this patient. The neonatal hemoglobin and hematocrit levels in this infant were within the lower limits of normal for cutaneous blood and suggested the possibility of losses d

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of fetal red cells into the maternal circulation.

O'Connor and associates¹⁰ found that hemolysates made from whole red blood cells taken from mothers in the immediate postpartum period contained fetal hemoglobin in 24 of 78 instances. The fetal hemoglobin present in the maternal circulation in their and in similar investigations is contained within intact and unhemolyzed fetal erythrocytes. No accurate observations are described in the literature involving the association of fibrinogenopenia and intravascular hemolysis with fetal hemoglobinemia maternal circulation, although Schneider¹⁴ has described fibrinogenopenia in the blood of a Group O adult who exhibited a hemolytic transfusion reaction from the receipt of 100 ml. of Group A incompatible erythrocytes.

Identification of the hemoglobin variant from lysed erythrocytes present in the maternal plasma in this case documented hemoglobinemia as due to destruction of fetal rather than maternal red cells. Further signs that this phenomena occurred in the maternal circulation are found in the characterization of the maternal anti-B isoantibody (Table II). A rise in titer of saline agglutinins 6 weeks post partum, the appearance of an "immune-type" anti-B agglutinin combined with an anti-B hemolysin is unequivocal serologic evidence of recent challenge and entrance of fetal Group B antigens into the maternal blood stream. The low titer of anti-B agglutinins in the 6 hour postnatal specimen and the absence of an anti-B hemolysin at that interval could be interpreted as temporary reduction in the maternal serum of these antibody components by their absorption on the surface of fetal erythrocytes.

Reilly and Zito12 have related the occurrence of a lowered quantitative fibrinogen in postpartum maternal blood samples to fetomaternal ABO incompatibility. These authors believe significant decreases in maternal fibrinogen are detectable in ABO heterospecific pregnancy as contrasted with ABO homospecific pregnancy. They do not explain exactly how fetomaternal incompatibility for ABO blood group antigens contributes to maternal defibrinogenation. In their studies, maternal fibrinogen values were never reduced within the hemorrhagic range shown in the case being reported.

Quick, Georgatsos, and Hussey¹¹ discovered that hemolyzed normal red cells may liberate a partial thromboplastin "clotting activity" after their destruction. McKellar and Dacie9 have shown that abnormal red cells, as those existing in patients with paroxysmal nocturnal hemoglobinuria, when studied in vitro can leak a phospholipid thromboplastic activity into their surrounding plasma even in the absence of significant lysis of these erythrocytes. It is evident from these investigations that red cells do possess several lipid materials with thromboplastic properties which might play some role in coagulation when there is intravascular red cell destruction. These observations, together with the events described in this paper, suggest an additional explanation for some instances of acquired fibrinogenopenia in pregnancy.

Since fetal red cells are forced into the maternal circulation in about one third of normal deliveries,3,10 probably from the dynamics of labor, it would follow that a tumultuous labor-as experienced by this patient—or a traumatic manipulation might result in penetration of larger numbers of fetal red cells into the maternal blood. In the presence of fetomaternal blood group incompatibility, if fetal red cells are met by a maternal antibody of a hemolytic variety, rapid lysis of moderate numbers of fetal red cells could be expected. The liberation of some intraerythrocyte product by such red cell destruction contributes to the development of lower nephron syndrome, as evolved in the patient studied and presented. Red cell phospholipids, also rapidly deposited in the maternal circulation, might initiate intravascular coagulation through a thromboplastic action. Defibrination of maternal blood might follow with development of fibrinogenopenia. A diagram of this possible set of sequences is seen in Fig. 2.

The likelihood that further obstetrical cases will be encountered, identical to the subject of this report, may depend upon the random occurrence of only certain fetomaternal blood group incompatibilities. The Rh and most other blood group isoantibodies are sensitizing rather than directly lytic in their in vivo reactions with their respective incompatible red cell antigens⁶ and would not be expected to incite maternal fibrinogenopenia through this hypothetical mechanism. Some examples of anti-A, anti-B, and anti-Lewis are the principal blood group isoantibodies with a proved ability to produce intravascular hemolysis.6 When a tumultuous labor is associated with those fetomaternal ABO or Lewis blood group incompatibilities in which a selective maternal isohemolysin exists, further instances of the phenomena found in this report may perhaps be reproduced.

Summary

In a pregnancy involving precipitous labor and ABO incompatibility, intravascular hemolysis, fetal hemoglobinemia, and fibrinogenopenia were demonstrated in the maternal circulation. Investigation suggested that lysis of fetal erythrocytes induced a temporary lower nephron nephrosis, and conceivably liberated thromboplastic activity to incite a maternal defibrination syndrome.

We are grateful to Leandro M. Tocantins, M.D., Director, The Charlotte Drake Cardeza Foundation, Division of Hematology, Jefferson Medical College, for his help in analysis of the fetomaternal hemoglobinemia. We are indebted to Mary B. Yelito, Special Hematology Laboratory, Harrisburg Hospital, for able technical assistance.

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Pelvic arteriography in obstetrics

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A LTHOUGH roentgenographic examination of various aspects of the vascular system was described more than a quarter of a century ago, there has been great reluctance until recently to make use of this valuable diagnostic tool. With the improvement in techniques and the development of safer, less toxic radiopaque contrast media came the rapid growth of these initially somewhat daring and spectacular procedures. There are few major vessels and organs in the body that cannot or have not been investigated by angiographic methods.

Aroused by the work of the Swedish investigators, notably Fernström¹ and Borell and associates,2-5 on the pelvic vasculature, we undertook this study to evaluate the usefulness of arteriography in obstetrical and gynecological diagnoses. As so often happens with new techniques, while investigating the diagnostic possibilities of arteriography from a purely morphological point of view, we found certain functional aspects were suggested. For example, visualization of the course taken by injected radiopaque material in the pelvic vessels of pregnant women stimulated interest as to the possible usefulness of arteriography in shedding some light on the circulation of the placenta.

One cannot discuss the historical background of pelvic arteriography without including the development of angiography in general, which dates back to the discovery of x-rays. In January, 1896, only 10 weeks after Roentgen's discovery of x-rays, angiography had its birth when Haschek and Lindenthal⁶ published the results of injecting the arteries of an amputated hand with an emulsion of chalk. Their paper included a photograph of the first arteriogram. In 1923, when Sicard and Forestier⁷ in France injected slowly 4 c.c. of iodized poppy seed oil (Lipiodol) into the antecubital vein of man and traced the flow of this material with a fluoroscope, the first attempt was made at angiography on a living subject. March, 1924, saw a great advance in technique and practical application of peripheral arteriography when Brooks8 published an account of the first successful arteriogram of the leg of a living person. He used a 100 per cent solution of sodium iodine injected through the exposed femoral artery and with the use of this substance clinical angiography was born.

The success of angiography in general is probably due more to the brilliant work of Reynaldo dos Santos,9 a Portuguese urologist, to whom goes the credit for the first successful translumbar aortogram. In 6 of his cases the uterine arteries were visualized. In one of these he was able to localize the placenta in a pregnant woman in the sixth month of pregnancy, and he suggested the possibility of visualizing tubal pregnancies in the same way. In more than 300 cases of abdominal aortogram done by the translumbar route he reported no fatalities. His report, however, was coolly received both in this country and in Europe. A further setback to angiography occurred when Henline and Moore,10 in

From the State University of New York Downstate Medical Center and the Kings County Hospital. 1936, published the results of injecting the aortas of 20 dogs with radiopaque substances and obtaining a 40 per cent immediate mortality due to hemorrhage and toxicity of the injected substances. They concluded that the procedure was, therefore, too dangerous to be used in human beings. Despite this, Allen and Camp¹¹ had performed over 100 arterial punctures in the study of peripheral vessels.

The first report in the American literature of an aortogram of a pregnant woman appeared in April, 1935, when Coutts and associates, ¹² of Havana, Cuba, were allowed to publish their findings in the American Journal of Obstetrics and Gynecology contrary to the Journal's policy at that time of not accepting contributions from foreign

sources. Because of the unusual character of these daring experiments the paper was accepted for publication. The radiographic findings were described but no mention of what happened to the patients was made.

With the outbreak of World War II progress in this field came to a standstill and even after the war not much was written until Hartnett, in 1948, reported his results after examining 68 pregnant women by translumbar aortography in various phases of pregnancy. He was able to diagnose 2 cases of placenta previa by this method. Most of these women were at or near term, and labor resulted in several cases after angiography. There was some question as to whether the procedure had something to do

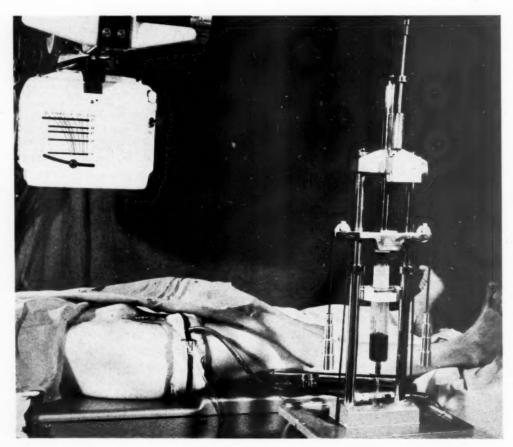


Fig. 1. Apparatus for percutaneous femoral arteriography. The automatic pressure injector is seen in the foreground with the contrast medium-filled syringe charged and ready for release by remote control. The control cord is seen in the right lower corner of the picture from where it is led out of the room; squeezing on a rubber bulb releases the trip lever compressing the plastic tubing and the contrast medium is discharged under pressure.

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Fig. 2A. S. R., 19 years old, was admitted with vaginal spotting at term. Arteriography showed a normally implanted placenta in the left lateral wall of the corpus. A metal clamp carefully inserted under direct vision marks the location of the cervix. Note the coiled arteries in the left upper quadrant arising from the uterine artery. Both sides are fairly well visualized with 35 ml. of contrast medium injected in 4 seconds. This film was taken 11/2 seconds after completion of injection. The patient was delivered of a normal infant 2 days later without incident. Final diagnosis, "bloody show."

with inducing early labor but he thought it more likely to be coincidence. No other fetal or maternal complications were noted.

Kunlin, Bitry-Boely, and Volnie,14 in 1950, and Guilhelm, Pontonnier, Enjalbert, and Baux, 15 in 1952, localized the placenta by visualizing the placental sinuses with direct aortic injection. No complications were reported. Smith, Evans, Elsey, and Felson¹⁶ examined 5 pregnant women near term, localizing the placenta in 3, and concluded that the procedure was safe and simple. No deaths occurred in 800 cases of translumbar aortography.

The Swedish group-Borell, Fernström, Lindblom, and Westman²—in 1952, wrote the first of a series of papers on retrograde percutaneous iliac arteriography, reporting on 101 obstetrical and gynecological cases. Sutton, 17 in 1952, and Norman, 18 in 1953, described the results of percutaneous puncture of the femoral artery in pregnant patients. In 1955 Fernström¹ published his monumental monograph on the entire subject of arteriographic examination of the iliac arteries and reported no complications after 700 injections in 448 cases including 59 cases of intrauterine pregnancy and 21 cases of tubal pregnancy. The safety and value of these procedures became well established.

The following essential equipment is required to visualize the pelvic vessels by arteriography: an ordinary x-ray tube set at 85 to 95 kv., 300 Ma., and 1/10 to 1/20 second and an automatic device for rapid changing of the cassettes so that serial films can be taken rapidly before dissipation of the contrast medium. In this study, the Sanchez-Perez automatic serialograph, capable of taking twelve 11 by 14 exposures at one-half second intervals, was used. A rectangular beam collimator concentrated the rays to the area examined with virtually no exposure to the surrounding tissues, and the use of fast



Fig. 2B. Taken 2 seconds after Fig. 2A. Note disappearance of opaque solution from larger vessels and the appearance of the arterial spurts or puffs in the left upper quadrant marking the location of the intervillous spaces.

Table I. Summary of 20 patients submitted to arteriography

Patient	Admission diagnosis	Final diagnosis	Arteriography result
R. R.	Placenta previa	Placenta previa	Unsatisfactory
H. K.	Placenta previa	Premature separation	Low implantation
A. C.	Ectopic pregnancy	Retroperitoneal hematoma	Failure (technical)
L. K.	Placenta previa	Intrauterine fetal death	Failure (technical)
О. Н.	Placenta previa	Marginal separation of placenta or possible marginal sinus rupture	Failure (technical)
M. W.	Placenta previa	Normal implantation	Failure (technical)
C. W.	Placenta previa	Placenta previa	Placenta previa
A. C.	Ovarian cysts, bilateral	Pregnancy in bicornuate uterus	Pregnancy in bicornuate uterus
L. B.	Placenta previa	Central placenta previa	Placenta previa
A. H.	Placenta previa	Normal implantation	Normal implantation
M. S.	Placenta previa	Premature separation	Normal implantation
R. M.	Placenta previa	Normal implantation	Normal implantation
D. N.	Placenta previa	Placenta previa	Placenta previa
V.H.	Placenta previa	Normal implantation	Normal implantation
B. F.	Placenta previa	Normal implantation	Normal implantation
M. C.	Ectopic pregnancy	Ovarian cyst (corpus luteum cyst)	No evidence of pregnancy
G. T.	Ectopic pregnancy	Intrauterine pregnancy	Intrauterine pregnancy
C. W.	Ovarian cyst	Ectopic pregnancy	Ectopic pregnancy
R. H.	Ectopic pregnancy	Ectopic pregnancy	Ectopic pregnancy
C. T.	Ectopic pregnancy	Ectopic pregnancy (left)	Ectopic pregnancy (left)
O. J.	Ectopic pregnancy	Pelvic abscess, bilateral chronic salpingo-oophoritis	No evidence of pregnancy
I. L.	Premature separation of placenta	Leiomyomata uteri	No evidence of pregnancy

film aided in decreasing radiation exposure to very low values.

The radiopaque material selected for this procedure was sodium and methylglucamine diacetylamino-triiodobenzoates* because of its exceedingly low toxicity and good contrast properties. This was injected through a specially devised Lindemann type of arterial cannula. The outer cannula, measuring 6.5 cm. in length, is equivalent in diameter to a No. 16 gauge needle. The inner cannula is equivalent to a No. 19 gauge needle and the puncturing needle which fits inside the inner cannula is a No. 22 gauge needle which is slightly longer than the cannula.

Percutaneous femoral artery injection (Fig. 1) is performed as follows: the patient, after the usual preparations for x-ray examination, is tested for sensitivity to the injected material by slow administration of 1 ml. of 60 per cent Renografin intravenously. In the average case Demerol, 100 mg., is given intramuscularly to allay apprehension and reduce

any discomfort of the procedure. The patient lies on her back on the x-ray table with the pelvis centered over the serialograph. The right or left femoral artery is selected for injection on the basis of the clinical findings, or, in the case of pregnancy, the choice is guided by auscultation of the placental souffle when present. After the area is cleansed and draped, the femoral artery just below the inguinal ligament is located by palpation with sterile technique and the local site anesthetized with 1 per cent procaine solution. A tiny nick is made in the skin with a sharp pointed knife to facilitate the passage of the special arterial needle. When the needle has entered the artery, blood is seen spurting from the open end of the cannula when the inner cannula is removed. The outer cannula is threaded well into the artery and attached by a 2 foot length of sterile polyvinyl plastic tubing to the syringe of the automatic injecting apparatus with Luer-Lok attachments. This syringe and tubing are filled with normal saline solution containing a few drops of heparin, and the apparatus and the cannula are flushed several

^{*}Sixty per cent Renografin, E. R. Squibb & Sons, New York. New York.

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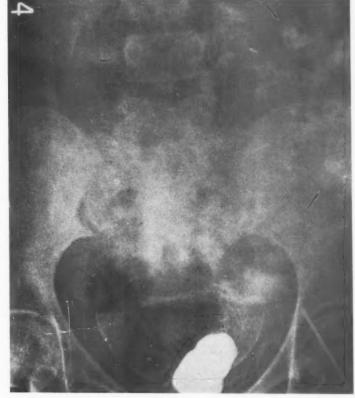


Fig. 3. V. H., a 32-year-old para 7-0-0-7, admitted for vaginal bleeding at the thirty-first week of pregnancy. The placenta is implanted on the left lateral wall. The opaque mass at lower edge of film is a sponge soaked in the contrast medium and carefully placed against the cervix under direct vision to indicate location of the cervix. The intervillous spaces are seen quite well 2½ seconds after completion of injection. The diagnosis was abruptio placentae with one third of the placenta separated. The infant was born alive and in good condition.



Fig. 4. D. N., a 23-year-old patient with placenta previa at 32 weeks of pregnancy which was confirmed at operation in the thirty-fourth week. A polyethylene catheter in the left iliac artery was threaded up to the aortic bifurcation. The arterial puffs are seen across the lower edge of the film after injection of only 5 ml. of Renografin.



Fig. 5A. A. C., a 24-year-old para 0-0-0-0 with a 10 weeks' gestation in the left horn of a bicornuate uterus confirmed at laparotomy. The left uterine artery is larger than the right.



Fig. 5B. Taken 3 seconds after Fig. 5A. The filled placental spaces are seen over the left side of the sacrum. Contrast medium is also noted in the capillary phase of the right uterine horn. This patient went on to term and was delivered of a normal 2,635 gram infant spontaneously. The placenta was located in the left horn of the uterus at the time of delivery.

times to insure good free flow and to check that the position of the cannula is well within the arterial lumen.

Pneumatic cuffs are fitted over both thighs as high up toward the groin as possible and inflated to obliterate the dorsalis pedis pulsations just before injection, so that the arterial circulation can be slowed somewhat. A preliminary scout film is taken to test the patient's position, the position of the cannula, and the exposure setting of the x-ray machine. At a given signal, 20 to 50 ml. of radiopaque material is injected by remote control from outside of the x-ray room at the rate of about 10 ml. per second under pressure of about 90 pounds per square inch. Exposures are taken usually at 1 second intervals starting just before completion of the injection with an average of 3 exposures taken in each case.

When the cannula is removed, continuous pressure is applied to the local area for 5 minutes or longer if necessary, and the patient is kept in bed for 8 to 10 hours to assure hemostasis. The blood pressure and peripheral pulsations are checked before and after injection, and no significant changes have thus far been noted.

Twenty femoral punctures were performed in 20 different obstetrical patients in various stages and with various complications of pregnancy. Although this report is concerned primarily with the results in this group of pregnant patients, we have also employed this technique in a wide variety of gynecological patients.

Findings in the 20 pregnant patients submitted to arteriography are shown in Table I. In this preliminary study no particular effort was made to select patients either for diagnosis or because they showed abnormalities, but rather to survey the possibilities of the technique as a diagnostic tool and as a research instrument for study of placental circulation. In the first category it quickly became apparent that the technique possessed several real possibilities. In the first place localization of the placenta is feasible and easy. Other than serving to localize the placenta, arteriography appears to be of value in the diagnosis of extrauterine pregnancy and also pregnancy associated with congenital uterine abnormalities.

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The appearance of the intervillous space filled with radiopaque substance is characteristic on the x-ray film and is easily recognized even by the inexperienced. The cotton ball configuration of the arterial spurts or "jets" noted also by Borell, Fernström, and Westman¹⁹ are seen very quickly after introduction of the contrast medium into the femoral artery under pressure. In some instances the coiled arteries are seen entering directly into these puffs, whereas the intervillous spaces seem to fill rapidly, drainage proceeds more slowly, and there is a delay before the radiopaque substance is dissipated. This can be appreciated by the persistence of the puffs on subsequent films many seconds later. However, there is no evidence that any sort of confluence occurs between neighboring intervillous spaces and there is no suggestion of a subchorial lake or common sinus into which the returning blood drains.

In instances of last trimester bleeding where the presence of placenta previa is suspected the ease of placental localization is well demonstrated in Figs. 2A, 2B, 3, 4, and 8. In these films not only are the "cotton ball" ends of the arterial spurts well demonstrated but the spinal arteries feeding them are seen. These are particularly striking in Figs. 8A and 8B.

Two abnormalities of gestation were demonstrated in this preliminary survey-one a pregnancy in the left horn of a bicornuate uterus and the other an ectopic pregnancy. In the first instance not only is the placenta seen but the vasculature of both uterine horns is clearly outlined (Figs. 5A and 5B).

The extrauterine pregnancy is easily diagnosed not only because of the absence of spiral arteries leading to the clearly visible placental sinuses but also because the coiled arteries in the small uterus are seen to be

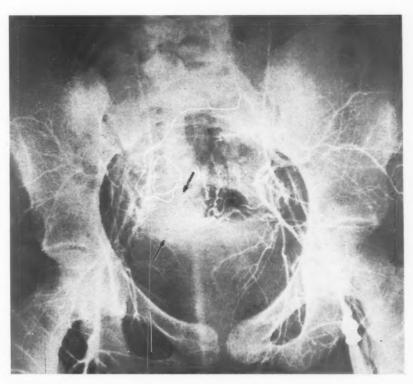


Fig. 6. G. T., a 23-year-old para 0-0-0-0 with a 6 weeks' intrauterine pregnancy confirmed at laparotomy for erroneously diagnosed tubal preg-- nancy. Both sides are filled with contrast medium. The coiled arteries are seen outlining the placental area. This patient when last seen was still pregnant.



Fig. 7. C. W., a 25-year-old para 0-0-1-0 with an unruptured left tubal pregnancy confirmed at laparotomy. The metal clamp in the lower center of the picture marks the location of the cervix. The bladder is filled with radiopaque medium from a test injection given several minutes before the arteriogram was started. The uterus is prominent because of its intramural and spiral vessels still containing opaque medium. The placental sinuses stand out clearly but absence of the coiled arteries leading into them is typical of extrauterine pregnancy.

quite independent from the placenta (Fig. 7). A very early intrauterine pregnancy is shown in Fig. 6. Although one can be quite sure of the intrauterine position of the placenta because of the usual arteriographic signs we, being amateurs at this type of diagnosis and strongly suspecting an extrauterine pregnancy, confirmed the arteriographic evidence at laparotomy.

As an instrument for research in placental circulation arteriography adds support to the contentions of Ramsey²⁰ regarding blood flow in the intervillous space. She believes that arterial blood spurts from the coiled arteries into the intervillous space under considerable pressure. When the flow is slowed by the villi, a pool is formed (cotton balls in arteriography) then the blood drains slowly to the basally distributed veins. These spurts number not more than 18 or 20. This is about the same order seen in our x-ray films. In

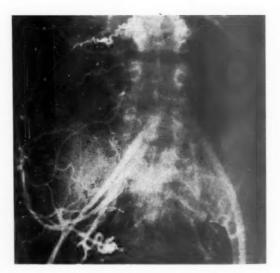


Fig. 8A. A. H., a 17-year-old para 2-0-0-2, was admitted with vaginal bleeding at the thirtieth week of gestation. The placenta is shown in the upper left fundal portion of the uterus as the arterial spurts are becoming visible.

contrast to Spanner's findings,21 the arteriograms show neither a subchorial lake nor marginal sinus drainage. While this is not proof of their nonexistence, it does raise a question which will have to be investigated.

In recent years the consequences of radiation exposure have become a major concern in roentgenology, particularly when pregnant women are involved. Keenly aware of this hazard, we took every precaution to reduce radiation dosages to a minimum. In this study a beam collimator was used to focus the x-rays on the desired area with virtually complete suppression of exposure outside of this area; a high speed film was used so that the time of exposure could be reduced to the barest minimum; and the number of films was held at 4 per patient, including a preliminary scout film.

In order for us to get some idea of the amount of radiation a patient receives during arteriography a group of patients was selected who were undergoing radiation therapy for carcinoma of the pelvic organs. These were divided into groups with thin, medium, and heavy pelvic density according to the anteroposterior diameter of the pelvis. With small dental x-ray film placed in the vagina and in the rectum, each was subjected to the same radiation conditions sustained by patients undergoing arteriography except that 5 exposures instead of the usual 4 were taken. The amount of radiation was measured by density studies of the exposed film, and the results were as follows:

Type of pelvis	to rectum	Radiation to vagina (mr.)
Thin (anteroposterior diameter 20 cm.)	250	210
Medium (anteroposterior diameter 24 cm.)	115	185
Heavy (anteroposterior diameter 27 cm.)	140	200

No significant complications were encountered in this series. A feeling of warmth spreading upward over the body was charac-

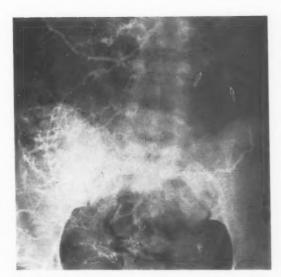


Fig. 8B. This film was taken 1 second after that in Fig. 8A. Careful examination shows coiled arteries entering directly into the intervillous spaces.

teristically experienced during the injection and for a few seconds after. A very transient wave of nausea occurred in about one third of the patients and vomiting occurred only once, but this was suspected to be due to the Demerol given just prior to examination. A slight soreness in the inguinal area at the injection site lasted about 24 hours but no more than for an ordinary venipuncture. Extravasation of the injected medium occurred in one of the earlier cases with no consequences and no symptoms.

Summary

- 1. A method of pelvic arteriography by percutaneous countercurrent femoral injection has been presented.
- 2. Twenty women in various stages of pregnancy were subjected to arteriography with no complications of note being encountered.
- 3. With the use of all known precautionary measures, radiation exposure need not be a serious problem.
- 4. Arteriography has been shown to be of value in localization of the placenta in both intra- and extrauterine pregnancies and can be used to distinguish between the two.

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- 5. This procedure can be used to obtain physiological information, such as the circulation of the placenta, as well as morphological data.
- 6. Arteriography is not advocated as a routine procedure, but in indicated cases which present difficult diagnostic problems this procedure may be of considerable value.

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The value of hysterography in the prediction of cesarean section wound defects

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AT PRESENT there is a relative complacency regarding the sequelae of cesarean section delivery. There has been a gradually rising rate during the past 10 year period. The well-known outstanding facts are that the maternal mortality from the operation has practically disappeared and the fetal salvage has improved with the rising rate. The invitation to perform cesarean section delivery is therefore freely accepted.

There is little doubt that the new decade will bring a still higher over-all rate and with this will come a still higher fetal salvage. The real effect on perinatal mortality is still debatable. The elimination of all traumatic vaginal deliveries will be sought and even the borderline forceps and breech deliveries will tend to disappear if the long-term morbidity of children is to be improved. A clearer understanding and detection of intrauterine anoxia will add impetus to the cesarean section rate. All this will not only increase the cesarean section rate in preference to these borderline traumatic deliveries but will involve more of what we at present refer to as "unnecessary cesarean sections." Eastman1 has clearly pointed out the futility of this term in that regrets stem from failure to perform a cesarean section rather than from performing too many.

A prediction of the acceptable rate in 10 years' time would neither be prudent nor, in itself, of any real importance. Some in-

dividual obstetricians have already arrived at the stage when cesarean section delivery is resorted to for all women deviating at all from the bounds of accepted normality. This policy quickly brings the rate up to 20 per cent or more. There are, furthermore, those enthusiasts who go almost the whole way in order to protect the pelvic floor and lower genitals from natural childbirth! For those who fear the cesarean section rate will "get out of hand," let me predict that this tendency will automatically be corrected by one factor—uterine morbidity.

Uterine morbidity should no longer be crudely judged by the incidence of uterine rupture subsequent to cesarean section. The thinking of the next decade should be more delicate. Till now the rupture rate has been a very rough yardstick of the subsequent ability of any uterus after a cesarean section. In an infinite number of publications rupture rates have been compared and debated with the general conclusion that the classical scar is more vulnerable than the lower segment scar.

Explosive or complete rupture

Assuming an equal degree of faulty wound healing in both a vertical fundal incision and a transverse lower segment incision, it is easy to imagine that during labor the weak fundal scar would be more likely to rupture than that in the lower segment. The fundal wound is unsupported and is in the strongly active section of the uterus. The lower segment is supported on all sides by hard and soft relations and is also in a less

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Fig. 1. Case A. Anteroposterior hysterogram showing dye escaping from left lateral end of cesarean section wound.

active part of the uterus, hence the incision here is less likely to explode than one in the fundal area.

Silent or incomplete rupture

There is an ever-increasing body of evidence to suggest that many lower segment wounds either heal defectively in the first instance or rupture incompletely and silently in a subsequent pregnancy or labor. It is also known that these minor wound deficiencies are capable of a "safe" vaginal delivery.

Recently, we have seen a patient who had a lower segment cesarean section with a hysterogram 6 months later showing a major defect. In her next labor, which was conducted elsewhere, she was allowed a vaginal delivery by an obstetrician with no knowledge of our hysterogram findings. There was apparently no cause for alarm during this labor. However, in the next labor she suffered a large uterine rupture through the lower segment wound. Baker² found 11 of 64 patients that he examined digitally after vaginal delivery following previous section to have deficient scars. Whatever the future holds regarding the relative merits of upper versus lower segment operations, of one technique as against another, or of subsequent vaginal delivery as compared with repeat cesarean section, it is certain that a more accurate measure of wound healing is required. Our experiences with hysterography have proved to us that the closer the examination the more deficient scars there are to be found.

Method of detecting scar weakness

A hysterographic technique has been devised and practiced since 1955, the method and results of which, to 1957, have already been published.³ The work to that stage showed that all uteri in the control series examined 6 months or more after vaginal deliveries presented a smooth, even contour. In 43 cases examined 6 months or more after cesarean section no case showed a



Fig. 2. Case A. Old wound deficiency in among scar tissue lateral to the left extremity of the present wound.

smooth, even contour. This 6 month wait is important, for an earlier examination may reveal no deformity owing to wound edema. Twenty-seven showed a fairly typical small wedge-shaped deformity which we have learned to associate with sound healing and which we believe to be safe in a subsequent vaginal delivery. Eleven showed larger deformities. (Five cases were left unclassified.) At that stage we had no knowledge of the subsequent fate of the 11 women with the large deformities. Since then, however, we have detailed evidence of 3 of them. One

has already been mentioned. One went to another clinic, which was unaware of our finding of a large retrovesical spread of dye; she was allowed to go into labor, and she suffered a severe rupture of the uterus. The third case is reported below:

Case A (Q.V.M.H., 11664). The patient was a 34-year-old gravida vii. Her first 5 pregnancies terminated in uneventful labors. The sixth was terminated in August, 1956, by a lower segment cesarean section, with a transverse uterine incision, for cervical rigidity resulting from a Manchester operation after her fifth child. The operator recorded that "great difficulty was experienced in suturing the left extremity of the uterine wound which had extended laterally into the broad ligament." There was postoperative pyrexia up to 101° F. for the first 2 days followed by a low grade pyrexia for the next 9 days, associated with a breakdown of the abdominal wound.

In February, 1957, a hysterogram was performed. Fig. 1 is an anteroposterior view showing dye escaping from the cesarean scar area out toward the left broad ligament.

She became pregnant again in June, 1958, and had a closely watched and uneventful pregnancy until near term when she noticed tenderness in the lower abdomen. On March 18, 1959, an elective cesarean section was performed by means of a transverse incision through the lower segment. After a baby weighing 9 pounds, 4 ounces, was extracted, an inspection of the lower



Fig. 3. Case B. Anteroposterior hysterogram showing wound defect with dye spill from left lateral end of scar. Note filling defect due to granuloma in the wound.

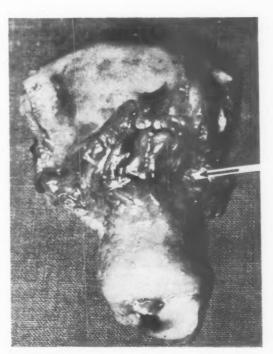


Fig. 4. Case B. The excised uterus. Arrow points to external appearance of wound defect.

segment was made; the findings are shown in Fig. 2. An old deficiency, in among scar tissue, can be seen lateral to the left extremity of the present wound. The tip of the gloved finger demonstrates the rounded edges of the hole.

This case shows to advantage the ease with which hysterography can demonstrate a uterine wound deficiency. The proof of its interpretation was provided by actual visualization of the deficiency at subsequent cesarean section. The poor wound healing in this case was due to a technical difficulty at operation together with a subsequent wound infection. The case also highlights the silence of such a deficiency during pregnancy, even to term, except perhaps for some lower abdominal tenderness which, in itself, is so notoriously difficult to interpret in late pregnancy. This case happened to be the only one in the original series of a large deficiency associated with a severe pyrexia. Since then, a closer relationship does seem to be showing up between severe pyrexia and large defects. However, many

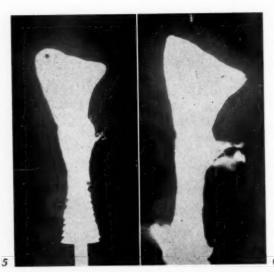


Fig. 5. Case B. Injection of radiopaque dye into specimen showing the early escape after 4 mils.

Fig. 6. Case B. Escape of dye after 6.5 mils had been injected.

cases show major deformities when no technical or postoperative difficulties were encountered.

Case B (Q.E.H., Maternity, 642). This case is one of the new series. The patient was a 30year-old gravida vii. Her first 6 pregnancies were uneventful. During her seventh labor in February, 1959, the umbilical cord prolapsed from a transverse lie and after considerable vaginal manipulation, in order to keep pressure off the cord, a lower segment cesarean section was carried out by means of a transverse uterine incision. Although there was considerable bleeding, requiring wound edge clamps, there was no great difficulty in repairing the wound in two layers with continuous No. 2 plain catgut. She subsequently developed peritonitis, paralytic ileus, and abdominal wound breakdown with prolapse of small intestine. The wound was resutured and healed cleanly. For the next 6 months she complained bitterly of pelvic pain and dyspareunia.

A hysterogram early in August, 1959 (Fig. 3), showed dye escaping from the uterus at the left end of the scar area. Another interesting finding radiologically was a filling defect diagnosed as a possible granuloma in the scar.

Because of the pelvic pain a total hysterectomy was performed after separation of adhesions. Both Fallopian tubes and ovaries were conserved. The bladder was adherent to the anterior cervix and required more stripping than usual. Fig. 4 shows the excised uterus with the arrow pointing to a defect in the cesarean section scar. Injection of dye shows an escape along the sinus at the left end of the old cesarean section scar (Fig. 5). As more dye was injected it was interesting to see it slowly escaping from the sinus (Fig. 6). The greater the pressure exerted the more dye spilled out. This sinus was easily found on opening the uterus (Fig. 7). The granuloma also became apparent on sectioning the uterus, and microscopy confirmed its nature and showed also the catgut still present after 6½ months (Fig. 8).

Comment

Two cases have been presented to demonstrate the value of the hysterogram after cesarean section. This method of investigation is capable of giving a detailed image of the uterine scar with little disturbance to the patient. No reason has been found to vary the technique from that previously reported. Further experiences are uncovering cases of scar deficiency even in women who have convalesced normally from operations relatively free of technical difficulty.

The greater our experiences with this form of investigation the greater has become the

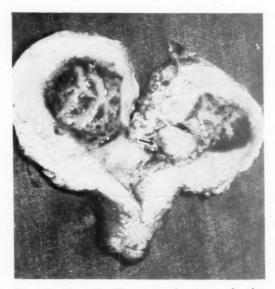


Fig. 7. Case B. The opened uterus showing granuloma in the scar and the position of the sinus at left end of the old wound.



Fig. 8. Case B. Section shows weak scar and much catgut still unabsorbed in the scar and both edges of the wound. (×6; reduced 1/3.)

conviction of the necessity and value of a hysterogram after cesarean section. It is an essential investigation to determine wound security. Any pouching effect, other than the commonly seen wedge-shaped deformity, indicates an escape of radiopaque substance through a sinus and the necessity for a repeat cesarean section.

Recently, Harris and Nessim⁴ surveyed the subject of cesarean section in a most convincing fashion. Their paper made no reference to uterine morbidity following the operation. No doubt their lack of interest in this aspect is covered by their following the dictum of "once a section, always a section." The communities which do not follow this dictum still need all possible information regarding wound security in order to arrive at a logical decision on the future conduct. Even for those who practice the 100 per cent repeat cesarean section policy it may still be wise to have knowledge of scar defects because complications of pregnancy are not unknown with such weak scars.

We all agree that traumatic deliveries must be eliminated and that this achievement will mean a higher incidence of cesarean section. This increasing rate should cause no alarm for, in itself, it is of no moment if it is productive of less fetal morbidity, but let us not neglect completely the fact that the uterus has been wounded. Good uterine healing is far from automatic with our present techniques. The disappearance of the manipulative obstetric art should not be mourned.

The next decade should see a more critical attitude toward the uterine wound, particularly as this group in the general population will continue to grow. A reassessment of operative techniques is indicated, and modifications will undoubtedly be attempted.

Summary

- 1. Greater consideration will be given to uterine morbidity after cesarean section in the next 10 years.
- 2. The rupture rate is a crude and inaccurate measure of uterine morbidity.
- 3. Reference is made to previous work which demonstrated the value of hysterography after cesarean section.
- 4. Evidence is now available on 2 cases of rupture of the uterus in which previous hysterography had demonstrated large defects; one patient had an apparently normal vaginal delivery in between the demonstration of the defect and the later rupture.
- 5. Another case is presented in detail showing the hysterographic demonstration of a defective scar subsequently confirmed at cesarean section.
- 6. A fourth case is given in detail to demonstrate a scar deficiency detected by hysterography and confirmed subsequently by examination after total hysterectomy.
- 7. A plea is made for a more critical appraisal of uterine wound healing after cesarean section.

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Combined paracervical and pudendal nerve blocks—a simple form of transvaginal regional anesthesia

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The direct causes of pain during childbirth are related to the intensification of uterine contractions and perineal distention with tissue trauma. Painfulness is indirectly enhanced by fears and emotional tensions. The relief of childbirth pain should therefore be directly applied to these causes. The minimal standards for accepting any procedure for relief of childbirth pain should include full safety to the mother and fetus and simplicity for its application.

Friedman¹ has shown that cervical dilatation in relationship to the lapse of time tends to have an established pattern. The "latent phase" (up to 3 to 4 cm.) may take twice as long as the rest of the first stage of labor. At this time the use of regional anesthesia retards the progress of dilation. Thereafter cervical dilatation is more rapid and is not impeded by regional anesthesia. Epinephrine in small doses, as used to prolong the action of anesthetic agents, can diminish or even stop uterine contractions during any stage of labor.²-⁴

Regional anesthesia during parturition

Thirty years ago regional anesthesia in obstetrics was regarded by Greenhill⁵ to be

very desirable. His original contentions have been sustained and are now highly recommended in the latest editions of well-known textbooks. 6-8 In a recent editorial review Greenhill⁹ enumerated many advantages of regional anesthesia during childbirth. He stressed its safety and simplicity and made a plea for its more frequent use in preference to inhalation or spinal anesthesia.

Transvaginal methods for pudendal nerve block have been recently described. The advocates of this type of pudendal nerve block consider it to be a simpler procedure. In the transperineal procedure the needle traverses a far greater distance through tissue in order to reach the target area where the anesthesia is injected. This is a more painful procedure, especially when it may be necessary to reinject the area. Kobak, Evans, and Johnson¹⁰ described their technique of transvaginal pudendal block, which was very soon followed by the descriptions of Wilds¹¹ and Dugger and associates.12 They all claimed equally good results although their techniques were somewhat different.

Much less attention has been given to paracervical anesthesia, which was presented by Rosenfeld.¹³ Whereas the pudendal block anesthesia is clinically applicable in the terminal phase of labor, the paracervical anesthesia is effective in relieving painful uterine contractions in the first and second stages. Freeman, Bellville, and Barno¹⁴ presented a large series (300 cases) wherein paracervical anesthesia was used. The ob-

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jections to this form of anesthesia have been the unpredictable occurrence of bradycardia in the fetus and the need of another anesthesia during the perineal stage of labor.

Recently we injected a radiopaque solution into the anatomic areas where pudendal and paracervical nerve blocks are administered. This interesting study revealed that there is a typical pattern for the dispersion of the anesthesia solution in the tissues, which will be described in another communication. This study reveals that all of the heretofore described techniques for paracervical and pudendal blocks have a very similar, if not identical, pattern of tissue spread. It explains why all the techniques for pudendal blocks can claim satisfactory results although differing in the manner of injection of the anesthetic solution. This has led us to discontinue the original method described by the senior author in 1956 and to simplify the transvaginal method by using a sheath to shield the point of the needle. The details of this modified instrument and technique will be described later in this communication. The spread of the anesthetic agent is along the path of least resistance in the tissue planes concerned, and this takes place instantly. Therefore, the use of hyaluronidase is not deemed necessary. The pattern of spread is upward and downward as well as posteriorly to the lumbosacral area. The pattern of spread in paracervical block is at a higher level than that seen in pudendal nerve area.

Recently Spanos and Steele¹⁵ presented a report on uterosacral blocks to give relief of pain in first stage. These blocks are obtained by injecting the vaginal fornix at 4 and 8 o'clock positions. The x-ray picture of the radiopaque solution injected in these positions reveals that this is obviously a paracervical block rather than a uterosacral one. There is a wide anteroposterior spread of the broad ligaments just above the lateral fornices of the vagina, especially during labor. When the needle point of penetration is positioned posteriorly at 3 and 9 o'clock, it nevertheless enters the broad ligaments as a paracervical block, as indicated by x-rays.

Procedure

Paracervical anesthesia is obtained by the deposition of the anesthetic solution into the paracervical tissues. The injected fluid then spreads into the broad ligaments and relieves the parturient from the pain of first stage uterine contractions. Our interest in this procedure was aroused by the article of Freeman, Bellville, and Barno¹⁴ in 1956. Our enthusiasm for transvaginal regional anesthesia prompted a trial of combining the paracervical and pudendal nerve blocks. When both of these nerve blocks are applied during the phase of accelerated cervical dilatation, they yield a tandem-like action whereby the relief from painful uterine contractions is followed by the necessary perineal anesthesia. It was soon apparent that this combined procedure yielded very satisfactory relief of childbirth pain. The report on our first 70 cases was presented in 1957 and was subsequently published in April, 1959.16 The study that is herewith presented consists only of cases in which the senior author personally delivered the patients at the Cook County Hospital and in private practice. All data that were deemed necessary were included in the protocol of every case.

The patients in this study were limited as far as possible to those with uncomplicated pregnancies in normal labor. This should include over 90 per cent of women in labor. The optimum time for paracervical block is during the accelerated phase of cervical dilatation. The presenting part is more often engaged, and the cervix, which is thin and effaced, has a tendency to be drawn up with each uterine contraction. The progress of labor is more rapid, the discomfort of the patient is considerably increased, and relief of pain is necessary. In order for the regional anesthesia to administered at this time, the doctor's personal supervision is necessary early

The materials that are essential in the administration of the paracervical and pudendal nerve blocks are the needles, the syringe, and the anesthetic agent.

Instruments

The instruments used for injecting the anesthesia consist of a 19 gauge, 18.5 cm. needle and a sheath of metal tubing of such length that it limits the distance of needle penetration to only 1.5 to 2 cm. It thus protects against any unintended tissue or glove penetration. A 20 c.c. Luer-Lok syringe is used to contain and inject the anesthetic solution. The limited distance of needle penetration is sufficient to obtain a paracervical or pudendal block. The instrument is designed to have a primary stop where the needle point is arrested just before the bulbous end, and, by rotation of the metal plate holding the hub end of the needle, parallel pins enter slots and the needle is advanced into the tissue to the limited 1.5 to 2 cm. distance.

Anesthetic solution

The anesthetic solution to be used should, ideally, spread well, have low irritancy, low toxicity, and adequate duration of effect. The problem of adequate anesthesia duration is one of great concern. In general, agents producing anesthesia longer than 60 to 90 minutes are the most toxic. In the manual on resuscitation of the newborn prepared by the American Academy of Pediatrics,17 regional anesthesia is evaluated and favored. "These agents, such as procaine, lidocaine, etc., cross the placenta as innocuous breakdown products, because they are hydrolyzed rapidly in the mother's blood. The main danger in their use is the production of hypotension or convulsions, both of which result from giving too much drug too fast."

A lapse of time between injections will tend to lower the concentration of the anesthetizing drug in the circulation. Thus, there will be a lesser possibility for adverse reactions. Ideally, 10 to 15 minutes should elapse between paracervical injections, and a shorter interval should be interposed between pudendal blocks. At the slightest signs of central nervous system stimulation or vascular depression, further injections should be withheld for at least 20 minutes.

More studies are needed to solve the problems of concentration and utilization of anesthetic solutions. A safe anesthetic agent that lasts 3 to 4 hours without danger of toxicity is presently not available.

In this study there were no major reactions from the anesthesia. Lidocaine,* 2 per cent, was the anesthetic agent of choice in the beginning of this study. In the first half of our study, 3 of the parturients exhibited evidence of disturbances, such as vague athetoid movements. We changed our anesthetic agent to a mixture of lidocaine and chloroprocaine.† This mixture consisted of 60 c.c. of equal amounts of 2 per cent of these anesthetic drugs. Chloroprocaine is currently regarded as the least toxic of agents available and produces nerve analgesia faster. Lidocaine, which has a longer sustained effect with a greater toxic potential, is now reduced to half the volume of the injected agent. By staggering the administration of this mixture, we have not noted even mild evidence of possible anesthesia reactions. Anesthetic agents were employed as follows: (1) lidocaine, 2 per cent, 10 c.c. to each paracervical and 7 c.c. to each pudendal area, or (2) lidocaine and chloroprocaine mixture (each 30 c.c., 2 per cent). For paracervical block 12 to 14 c.c. on each side; for pudendal block 10 c.c. on each side. This anesthesia mixture is preferred.

Technique

A. Paracervical block. The site of injection is the junction of the lateral walls of the cervix with the vagina. Needle penetration is approximately at the 3 and 9 o'clock positions (Fig. 1). We prefer to inject the left side first and, after an interval of 2 uterine contractions, the right side. After the first paracervical injection, the next uterine contraction is definitely less painful and is felt mainly in the uninjected side. It is preferable to allow an interval of 2

^{*}Xylocaine, Astra Pharmaceutical Products, Inc., Worcester, Massachusetts,

[†]Nesacaine hydrochloride, Maltbie Laboratories Division, Wallace & Tiernan Inc., Belleville, New Jersey.

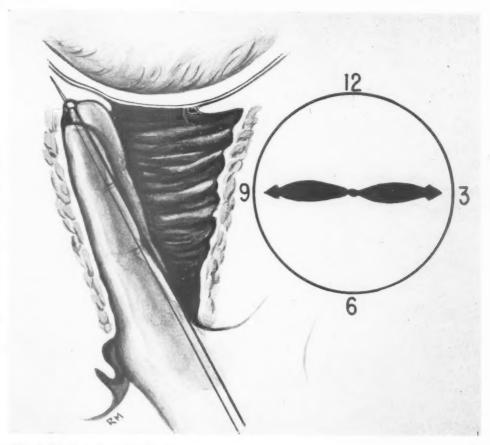


Fig. 1. Right paracervical block.

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uterine contractions before another injection of anesthesia in order to avoid concentrating the amount of injected material. When paracervical anesthesia develops, most patients become unaware of uterine contractions.

B. Pudendal nerve block. When the paracervical anesthesia adequately relieves the pain of uterine contractions and cervical dilatation is nearly complete, the pudendal nerves are blocked. The left ischial spine is felt with the left index finger (Fig. 2). The needle retracted in the sheath is then inserted into the vagina, directed by the fingertip of the palpating left hand. The bulbous bead of the sheath is directed against the area of the vaginal wall that is immediately under the spine, and the needle point is inserted therein. The syringe is attached to the needle and, if preliminary aspiration yields no blood, the drug is injected. If blood

is aspirated, the needle point is moved more medially, i.e., closer to the nerve trunk.*

When lidocaine, 2 per cent, is used exclusively, we inject 7 c.c. of this agent. The first 5 c.c. is injected with the needle fully penetrated and the last 2 c.c. with the needle partially retracted. When mixed with chloroprocaine a total of 10 c.c. is injected and the last 3 c.c. of the solution is given with the needle partially retracted. The perineal area is then tested for the development of anesthesia. When this develops there will be absence of the anal sphincter reflex, and no pain will be felt by needle pricking or hemostat pinching.

^{*}Prior to injection, the area is routinely aspirated. During active labor the formation of the lower uterine segment increases the distance of the large uterine vessels from the top of the vaginal vault. Aspirated blood is often obtained in pudendal nerve blocks but rarely in the paracervical area. No epinephrine is used.

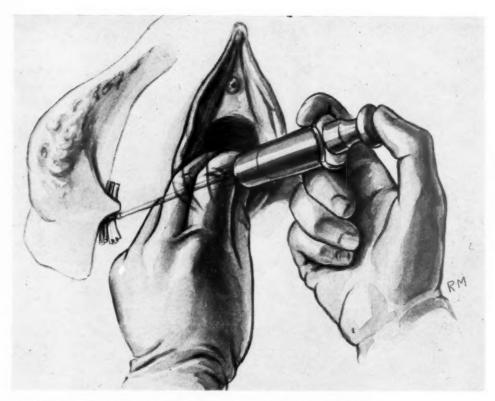


Fig. 2. Right pudendal nerve block. (The text describes a left side block.)

Results

One hundred patients were given paracervical and pudendal nerve blocks for purposes of pain relief. All of our patients were delivered by regional anesthesia. Immediate relief of pain and cervical dilatation continued after the administration of paracervical nerve blocks. The assessment of pain relief is not an easy one. The separation of apprehension from true pain is sometimes difficult. Our results were graded as excellent if the uterine contractions continued painlessly after the administration of the nerve blocks (Table I). The relief in 71 parturients was thus graded as excellent. It was graded good (29 patients) when the contractions caused only slight discomfort that was readily tolerated. Frequently the residuum of discomfort was due to apprehension. All of our patients had pain relief that was considered to be good or excellent. The results in accordance to parity were as follows: among 44 primiparous women the gradings in 32 (73 per cent) were excellent; of 56 multiparous women the results were excellent in 39 (69.6 per cent).

The use of ancillary sedation was distributed as shown in Table II. Analgesic medication was administered to 42 patients. The amount of meperidine* given was usually limited to only one 50 mg. intravenous injection. Meperidine was administered to 37 patients prior to the nerve block. Recently phenazocine† was used in 5 cases. Forty-one patients received no premedication, and 17 were given only mepazine‡ or promethazine§ for tranquilizing sedation.

The termination of labor (Table III) was spontaneous in 48 patients. Forceps were

*Demerol hydrochloride, Winthrop Laboratories, New York, New York.

†Prinadol, Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

‡Pacatal (N-methyl piperidyl-3-methyl phenothiazine), Warner-Chilcott Laboratories, Morris Plains, New Jersey.

§Phenergan hydrochloride, Wyeth Laboratories, Philadelphia, Pennsylvania.

used to terminate the labor of 50 parturients. While pudendal block plays a most important part at this time, there is reason to believe that it also helps to fortify the effects of the paracervical block. However, more case study is needed to verify this statement. Most of the low or outlet forceps were electively applied. Forceps application was also influenced by the concern for the maintenance of an adequate perineal anesthesia in order to repair the perineum. In our study pudendal block gave sufficient anesthesia for all procedures needed to terminate labor, whereas Spanos and Steele¹⁵ found it necessary to use other types of anesthesia to terminate labor in almost half of their cases. We attribute this difference to our use of transvaginal pudendal block only as the second stage of labor was approaching.

Resuscitation of the fetus was necessary in 8 instances. In 2 patients the asphyxia was considered to be due to the epinephrine that was used with the anesthesia. In 4 instances midforceps were used, and in 3 of these cases Dührssen's incisions were made. In 3 instances the fetal distress was present prior to the use of paracervical blocks, and when the fetal heart tones had stabilized to a normal rate paracervical blocks were administered. There was only one fetal death among the 100 patients who were given these transvaginal blocks. In this patient the fetal heart tones were normal but the amniotic fluid had a meconium tinge. After an easy forceps delivery spontaneous respirations did not occur, nor could they be stimulated by resuscitation. This baby had marked hepatomegaly and signs of Mongolism. Its death was regarded as unrelated to the use of local anesthesia. The respirations in all other babies were characterized by a normal spontaneous onset, and in most instances the baby began to breathe or cry before it had completely emerged from the vagina. Spontaneous breathing with a lusty cry was the usual sequence of events.

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The analysis of cervical dilatation following paracervical administration of anesthesia was very interesting. A pilot study was previously made in a small series, with control

Table I. Relief of pain

	Total	Primiparas	Multiparas
Total	100	44	56
Excellent	71	32	39
		(73%)	(69.6%)
Good	29	12	17

Table II. Ancillary medication

Total patients	100
No premedication	41
Tranquilizing medication	
(before blocks)	17
Analgesic drugs (before blocks)	42
Meperidine, 50 mg.	37
Phenazocine	5

Table III. Termination of labor

Patients delivered		100
Cephalic presentation	98	
Spontaneously delivered 48	1	
Forceps 50)	
Low 35		
Mid 15 (with rotation, 9)		
Breech presentation	2	
Incomplete breech extraction,		
forceps to aftercoming head		
Complete breech extraction		
(prolapse of cord)		
Miscellaneous		
Dührssen's incisions	3	
(fetal distress present prior to para-		
cervical blocks in 2 patients)		
Perineorrhaphy		2
Prematurity of fetus		4
(low forceps used in 3)		
Resuscitation		8
3 included in Dührssen's incisions		
(Item 2); only 1 case directly due to regional anesthesia (epinephrine)		

Table IV. Time lapse to complete dilatation after paracervical nerve block*

	Entire series (%)	Without epineph- rine (68 cases) (%)	With epi- nephrine (29 cases) (%)
Within 30	44.9	47	20
minutes	44.3	47	38
Within 1 hour Within 1½	75.2	82.3	58.6
hours Longer than	90	95.6	75.8
1½ hours	10	4.4	24.2

^{*}Three patients having Dührssen's incisions not included.

cases in which cervical dilatation was approximately the same as determined by vaginal examination. The findings indicated that the cervix apparently dilated faster after a paracervical block. The lapse of time for full dilatation of the cervix after paracervical injection of anesthesia was analyzed (Table IV). From this table it is apparent that cervical dilatation proceeds fairly rapidly. It is fastest when the paracervical block is administered closer to full dilatation. As expected, the cervix of the multiparous patient dilates faster than that of the primigravida. Due to the rapidity of cervical dilatation the majority of our patients were given a paracervical block and then kept on the delivery table until labor was terminated.

Effect of epinephrine

In the first 32 cases of combined paracervical and pudendal blocks, epinephrine was included in order to prolong the anesthesia. The use of epinephrine was frequently followed by a decrease in the intensity of the uterine contractility. In most of the cases this amounted to a complete but temporary cessation of contractility. Dilatation of the cervix was slower when epinephrine was included, especially among primiparous parturients (Table IV). One may conjecture that some of the relief of pain, when epinephrine was used, was partially due to the temporary cessation of contractions. However, epinephrine may unpredictably give rise to fetal bradycardia. The fetal heart tones in 5 of the 32 cases where epinephrine was used, slowed down almost immediately after the paracervical administration of anesthesia. We therefore decided to discontinue its use. Thereafter, bradycardia was not noted, the pain relief was equally effective, and the progress of labor was faster.

Comment

This study demonstrates simple procedures that can relieve the pain of parturition. When integrated with other safe procedures and used at the proper time in the course of labor, the combined paracervical and pudendal blocks have been found to be safe and reliable. A substantial number of private patients in this study were emotionally prepared during the prenatal period. Suggestive therapy was the vehicle of inducing relaxation in these patients, and they were unmindful of discomfort during the latent period prior to paracervical pudendal blocks. It was shown in our study that the accelerated phase of cervical dilatation, particularly after 4 cm., is the optimum time for the application of the combined transvaginal nerve blocks. This is the period when pain frequently becomes unendurable. Tranquilizing and analgesic drugs have their limits in safety. More than half of our patients had no need for narcotic drugs. The use of regional anesthesia was welcomed by all patients. The relief was an immediate one. A single application sufficed in a significant majority of patients.

A problem still to be solved is the means of dealing with cervices which are slow in dilating after paracervical injection of the anesthetic drug. Lest the nerve block wear off, Pitocin is deemed necessary in patients having inadequate uterine contractions. A longer-acting safe anesthesia is not known.

Conclusions

Relief of pain was obtained in all of the 100 patients who received regional transvaginal anesthesia. The administration of anesthesia is simple, and it is safe for the mother and/or the baby. The optimum time for the administration of paracervical blocks, which are followed by pudendal nerve blocks, is after a 4 cm. cervical opening with indications that this dilatation is continuing. By the use of an instrument protected by a sheath to guard against unintentional tissue penetration or damage from rubber gloves, the above procedures are remarkably simplified. Epinephrine is contraindicated in paracervical blocks. By staggering the administration of the anesthesia agent, reactions are prevented. The pudendal blocks are withheld until the uterine contractions have become painless and the cervix is approaching full dilatation.

Addendum. In the interval between the reading and the publication of this article, some significant changes were adopted by the authors.

The instrument that was described was changed by its simplification without altering its effective-

ness. The combination of two anesthetic agents has been discontinued, and in its place we are using a recently available anesthetic agent, mepivacaine,* that gives satisfactory safety and has a longer period of effectiveness.

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Discussion

Dr. E. Trier Mörch, Chicago, Illinois. This paper describes a simple and practical technique and leaves me only minor technicalities to discuss.

The term "anesthesia" ought to be reserved for conditions where the patient is asleep. "Analgesia," meaning absence of pain, is preferable for procedures such as the ones under discussion.

It is not clear why the authors use a mixture of Xylocaine and Nesacaine, both potent, fast-and short-acting analgesics. Nesacaine alone might be too short-acting, but Xylocaine alone would probably give the same good results.

The total amounts of anesthetic agents used seem high. Xylocaine 1 per cent is sufficient and far safer than 2 per cent solutions; it is safer to use a lower concentration, even if the volume has to be increased. The most important single factor is the absolute amount, which for Xylocaine should not exceed 500 mg. injected over 30 minutes, or 50 ml. of a 1 per cent solution (or 25 ml. of a 2 per cent solution).

Dr. S. R. M. REYNOLDS, Chicago, Illinois. This paper raises many interesting physiologic

questions. Of these, I have picked two or three to call to your attention.

Hardy and Wolff studied the sensitivity of women in labor to pain. They found that as the cervix dilates the pain threshold becomes low. The sensitivity to a painful stimulus applied to the skin increased as the pressure on the cervix increased. This has been defined as "dolr." It decreases as labor progresses. This raises a question as to how the cervix modifies somatic pain. These same results are found when labor is stimulated by Pitocin. The cutaneous pain threshold diminishes as the cervix dilates.

The sensory receptors in the cervix extend up to the level of the external os. That is why the cervix is so sensitive to stretching. What physiologic purpose is served by the stretch reflex of the cervix? From the literature, based on experiments in animals, one sees examples of the effect as the cervix becomes rapidly dilated in the first stage of labor. Since the cervix is stretched little at first, the posterior pituitary body does not come into play during the first part of the labor. Later, the neurohypophysis

*Carbocaine, Winthrop Laboratories, New York, New York

causes endogenous secretion of Pitocin. The painful effect of stretching the cervix is what Dr. Kobak wishes to eliminate. To do so will surely eliminate a physiologic component of normal labor. It occurs to me that one reason the authors used forceps was perhaps because in addition to knocking out pain the drug knocked out the cervical stretch reflex.

The reason why epinephrine has such a bad effect when given with Xylocaine is that epinephrine in very small quantities infused into the antecubital vein of a woman has a profound inhibitory effect upon the uterus. When a fraction of a gamma of the substance enters the blood stream and mixes with the blood, only a small portion of it reaches the uterus. Norepinephrine has an opposite effect. It stimulates the uterus. Such results explain not only why epinephrine will produce the symptoms Dr. Kobak speaks of, but also why it stops uterine contractions and delays labor.

There is another side to this problem. When blood is taken during uterine diastole from a woman in labor and analyzed for epinephrine, interesting results are found. Women who require no sedation have no measurable epinephrine. Women who are tense and request sedation late in labor have measurable epinephrine and in women who have uterine inertia the blood epinephrine levels become four times as high. Epinephrine, whether endogenous or exogenous, has an adverse effect upon the uterus.

DR. J. P. GREENHILL, Chicago, Illinois. Most of you know my attitude about the use of spinal anesthesia in obstetrics. I advocate local anes-

thesia because it is the safest of all anesthetics and because it has numerous other advantages over spinal anesthesia. However, not all pregnant women are proper candidates for direct infiltration, nor are all obstetricians temperamentally suited for this type of anesthesia.

Dr. Kobak uses two types of local anesthesia, paracervical and pudendal. Apparently, the paracervical anesthesia is helpful both for relief of pain and for shortening labor. May I again make a plea that in obstetrics we should use less spinal and more local infiltration anesthesia.

Dr. Kobak (Closing). When Demerol was administered it was given prior to the paracervical block. The pain relief subsequent to the administration of the paracervical block precluded the necessity of administration of analgesic drugs. Recently, we have used phenazocine, a sedative presently not available commercially. It is likely to take the place of Demerol because of its potential for far greater relief of pain with far less depressant action on the mother or fetus.

In mixing Nesacaine and Xylocaine (lidocaine) we dilute and diminish the amounts of the latter. By staggering the administration we avoid the possibility of massive intravenous absorption and potential reactions. In the study herewith presented there were no cases of anesthesia reaction, and we never noted any convulsions.

There could be no doubt at all concerning good pain relief resulting from the procedures we used. In 71 per cent it was deemed excellent. Our private patients who were emotionally prepared during the prenatal period showed the better results.

Prematurity and illegitimacy

ARTHUR H. PARMELEE, JR., M.D.

Los Angeles, California

OF PARTICULAR interest for this study is the fact that the incidence of prematurity is generally reported to be higher among unmarried mothers than in the general population. Raiha¹ gives an incidence of 15.7 per cent premature births among unmarried mothers in Finland as compared with 5.1 per cent among "housewives at home" and 14.0 per cent among "housewives with outside work." In Great Britain2 the incidence of premature births among illegitimate births was 9.7 per cent compared with an incidence of 4.3 per cent among infants born to wives of professional and salaried workers and 6.5 per cent among other wage earners. Blegen³ reports an incidence of 12.8 per cent prematurity in illegitimate pregnancies in Norway as compared with 6.1 per cent for legitimate pregnancies. Others reporting an increased incidence of prematurity in illegitimate pregnancies are Crosse,4 Norregaard,5 Crawford,6 Toverud,7 and Drillien.8 In a recent study Stevenson9 found that the incidence of prematurity was not greater in illegitimately pregnant white women when compared with a control group, but the incidence of prematurity was increased among illegitimately pregnant Negroes.

The over-all incidence of prematurity in the United States is reported by Dunham¹⁰ to be 7.4 per cent of live births. For white infants this drops to 7 per cent and for Negro infants it rises to 9.7 per cent. The exact incidence will vary, depending on the geographic location and other circumstances.

A study of prematurity in California was performed in 1949.¹¹ The over-all incidence of premature births was 6.9 per cent of live births. In county hospitals in California, the incidence of premature births was 9 per cent as compared with 6.4 per cent in other tax-supported hospitals and 6.5 per cent in private hospitals. The total incidence of prematurity in the Los Angeles area was 7.2 per cent of live births. A Los Angeles City Health Department study of prematurity in 1950¹² reported an over-all incidence of 7.7 per cent with an incidence of 7.1 per cent for whites, 12.3 per cent for Negroes, and 8.9 per cent for others.

The causes of prematurity are unknown but many factors have been found to be related to a higher incidence of prematurity. The age of the mother would appear to be significant with the incidence of prematurity reported to be higher in mothers under 20 and over 40 years of age.1, 2, 4, 10, 13 Prematurity is also reported to be more frequent in primiparous than in multiparous mothers.1, 2, 4, 5, 18 Socioeconomic factors play some role since prematurity is found to be more common among the lower classes and the poor.2-4, 10, 13-15 Complications of pregnancy, particularly toxemias, are definitely associated with an increased incidence of prematurity.1, 2, 10, 15 Female infants tend to weigh less than male infants and hence fall into the premature weight category more frequently,4,8,10 and multiple pregnancy is associated with a very high incidence of premature births.3, 4, 10 (The relationship of illegitimate pregnancy to prematurity has already been discussed.)

Conversely, there is some evidence that early and adequate prenatal care that in-

From the Department of Pediatrics, University of California at Los Angeles Supported in part by a grant from the Mead Johnson Company. cludes improved maternal nutrition, more rest in the latter part of pregnancy, and the prevention of toxemias, is associated with a decreased incidence of prematurity.^{2, 4, 7, 10, 15} This implies that inadequate prenatal care and poor nutrition are associated with an increased incidence of prematurity.

Many reasons for the higher incidence of prematurity among illegitimate pregnancies have been suggested, such as the younger age of the mothers, the greater incidence of primiparous births, and the poor socioeconomic status of the mothers and consequent inadequate medical care and poor nutrition. The factors of the youth of the mothers and the primiparous births cannot be altered but it could be postulated that if the unwed mothers received adequate prenatal care and nutrition in a favorable environment, the incidence of prematurity might be reduced.

This investigation was prompted by a previous study carried out at the St. Anne's Maternity Hospital of Los Angeles by Von Der Ahe and Bach¹⁶ on the course of pregnancy in 136 young girls, 12 through 16 years of age. In this group there were 8 premature infants, an incidence of 5.9 per cent. These authors also found a surprisingly low incidence of other complications of pregnancy as compared with other reported studies of pregnancies in young girls. They emphasized the fact that the antenatal care these girls received may have played an important role in preventing prematurity and other complications of pregnancy. This suggested that the fact of illegitimacy or the youth of the illegitimately pregnant mothers was not in itself a cause of prematurity.

It then seemed advisable to study the incidence of prematurity among all of the mothers delivered at the St. Anne's Maternity Hospital for a period of time. Presumably, if all the mothers were receiving good prenatal care, the incidence of prematurity would be within a normal range for the Los Angeles area.

Material and methods

St. Anne's Maternity Hospital in Los Angeles is a Catholic hospital for illegitimately

pregnant women. These women come from all over the United States, either on self referral or on referral by agencies and doctors. They are charged for the cost of their care according to their ability to pay. Many live in the home connected with the hospital and do work in the hospital or home to help pay their expenses. Some who plan to be delivered in this hospital live in boarding homes or hotels and others, who are from Los Angeles, live in their own homes. All attend the prenatal clinic at the St. Anne's Maternity Hospital. They attend once a month until the last trimester when they attend every 2 weeks. Some come to the hospital at term, having received prenatal care elsewhere or no prenatal care at all.

The records of this hospital were reviewed for the period from Jan. 1, 1949, through Dec. 31, 1952. The following items were tabulated on I.B.M. cards for future analysis:

- 1. Age of the mother at the time of registration in the clinic.
- 2. The marital status of the mother at the time of the illegitimate pregnancy. This was coded as single, divorced, separated, married, or widowed.
 - 3. The parity of the pregnancy.
- 4. The race of the mother. This was coded as white-not Mexican, white-Mexican, Negro, and other, including Japanese and Chinese.
- 5. The education of the mother was listed as grammar school, high school, or college. Attendance for one year in high school or one year in college was enough to place the mother in this category for coding.
- 6. The residence of the mother during the last trimester of pregnancy. This was coded as St. Anne's Maternity Home, mother's own home, or other.
- 7. The trimester of pregnancy when the mother first started receiving prenatal care at the St. Anne's Maternity Hospital Clinic.
- 8. The estimated economic status of the mother based on the amount she was requested to pay for her hospital care. Those who paid the full price were listed as of high economic status, those who paid their own way but received some reduction in the fee

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charged were listed as of average economic status, and those who paid nothing or who had an agency paying for their care were listed as of low economic status.

9. Complications of pregnancy as indicated by the attending physician. This category included hypertension, toxemia, vaginal bleeding, known acute illnesses, and other complications of pregnancy. The type of complication was not coded.

10. The sex of the baby.

11. The baby's birth weight. Babies weighing 5 pounds, 8 ounces (2,500 grams) or less were classified as premature and those weighing more than this as full term.

12. The placement of the baby. Some mothers kept their babies; other babies were placed in adoption and some were placed with relatives or friends. This latter was coded as other.

The recorded data were analyzed first for the incidence of prematurity for all births, live births, live single births, and multiple births. The incidence of prematurity for all live births was then compared with comparable data for the United States, California, and Los Angeles.

Then the additional data were analyzed by comparing the data on the mothers of term infants with similar data on the mothers of premature infants. An effort was made to determine the factors contributing to prematurity among the mothers delivered at St. Anne's Maternity Hospital.

Results

During the period of investigation, from Jan. 1, 1949, through Dec. 31, 1952, there were 1,024 mothers registered for delivery at St. Anne's Maternity Hospital. Thirty-six of these mothers were transferred to other hospitals for delivery because of some complication of pregnancy. Complete records of the pregnancy, delivery, and birth weight and condition of the baby were available in 17 of these cases. In 14 additional cases, data on the mother were incomplete but the birth weight and condition of the baby were known. All of these were full-term babies, weighing more than 5 pounds, 8 ounces. For

the remaining 5 mothers registered, there was no record of a delivery.

Thus, of the 1,024 mothers registered, the outcome of the delivery and the birth weight of the child was known for 1,019 (Table I). There were 1,044 babies born to these mothers. This number includes 25 sets of twins. The total number of babies weighing 5 pounds, 8 ounces or less was 81. Therefore, the total incidence of prematurity for 1,019 deliveries was 7.9 per cent and for 1,044 births, 7.8 per cent.

There were 10 stillborn babies, including one set of twins. One stillborn baby weighed 5 pounds, 8 ounces or less. Therefore, the incidence of live premature births (80) for 1,034 live births was 7.7 per cent.

There were 984 single live births and, of these, 62 were single live premature births. Therefore, the incidence of prematurity for single live births was 6.3 per cent.

There were 18 liveborn babies of twin births weighing 5 pounds, 8 ounces or less (premature) among the 48 liveborn babies of twin births. The incidence of prematurity for twin births was 37.5 per cent.

A comparison of the total incidence of prematurity among live births at St. Anne's Maternity Hospital with those reported for the United States, ¹⁰ California, ¹¹ and Los Angeles ¹² reveals no statistically significant difference between any of these populations (Table II). Thus, the original impression that the incidence of prematurity among the illegitimately pregnant women at St. Anne's Maternity Hospital is not increased over that of the general population is substantiated.

The additional data on the mothers delivered at St. Anne's Maternity Hospital were analyzed in an effort to determine those factors that contributed to premature delivery in this particular population.

Of the 1,019 mothers for whom the outcome of the delivery and birth weight of the baby were known, the records were complete enough for further study on 1,005 mothers and their 1,030 infants (Table III). The 25 sets of twins and the 81 infants weighing 5 pounds, 8 ounces or less were all in this

Table I. Analysis of total census at St. Anne's Maternity Hospital from Jan. 1, 1949, through Dec. 31, 1952

Total number of mothers registered for delivery from Jan. 1, 1949, through Dec. 31, 1952	1,024
Total number of mothers with no delivery recorded	5
Total number of mothers with record of delivery and birth weight of the baby recorded	1,019
Total number of babies born (this includes 25 sets of twins)	1,044
Total number of infants with birth weights of 5 pounds, 8 ounces or less (premature)	81
Number of stillborn infants weighing more than 5 pounds, 8 ounces	9
Number of stillborn infants weighing 5 pounds, 8 ounces or less (premature)	1
Total number of live births	1,034
Number of liveborn premature infants	80
Number of babies of twin birth weighing more than 5 pounds, 8 ounces	32
Number of babies of twin birth weighing 5 pounds, 8 ounces or less (premature)	18
Number of single births	994
Number of single live births	986
Number of single liveborn births of babies weighing 5 pounds, 8 ounces or less	62
Total incidence of premature births (81) for 1,019 deliveries	7.9%
Total incidence of premature births (81) for 1,044 births	7.8%
Total incidence of liveborn premature births (80) for 1,034 live births	7.7%
Total incidence of liveborn premature single births (62) for 986 single live births	6.3%
Total incidence of liveborn premature twin births (18) for 48 live births	37.5%

Table II. Comparison of total incidence of prematurity among live births at St. Anne's Maternity Hospital with United States, California, and Los Angeles Statistics

Location	Location Total No. of live births		Incidence of prematurity*	
1. St. Anne's Maternity Hospital Jan.				
1, 1949, to Dec. 31, 1952	1,034	80	7.7%	
2. Los Angeles, 195012	39,641	3,053	7.7%	
3. California, 1949 ¹¹	244,084	16,893	6.9%	
4. United States				
January-March, 195010	837,786	61,637	7.4%	

^{*}There is no significant difference between 1 and 2, 3, or 4 at the 5 per cent level of confidence.

Table III. Analysis of complete record on mothers and babies registered at St. Anne's Maternity Hospital from Jan. 1, 1949, through Dec. 31, 1952

Total number of mothers delivered with complete records including babies' weight and	4.000
condition	1,005
Total number of babies delivered	1,030
Total number of twin births	50
Total number of single births	980
Total number of stillbirths (includes one set of twins)	6
Total number of live births	1,024
Total number of babies weighing 5 pounds, 8 ounces or less	81
Total number of liveborn babies weighing 5 pounds, 8 ounces or less	80
Total number of single live births	976
Total number of single liveborn babies weighing less than 5 pounds, 8 ounces	62
Incidence of prematurity (81) for 1,005 deliveries	8.1%
Incidence of prematurity (81) for 1,030 births	7.9%
Incidence of prematurity (80) for 1,024 live births	7.8%
Incidence of prematurity (62) for 976 single live births	6.4%

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group. Five of these mothers were delivered of 6 stillborn infants (this includes one set of twins); one of these weighed 5 pounds, 8 ounces or less. Thus, 1,000 mothers were delivered of 1,024 liveborn infants, of whom 80 weighed 5 pounds, 8 ounces or less and, therefore, were considered premature. Of these latter, there were 976 liveborn single births. Sixty-two of these were liveborn premature infants.

The total incidence of prematurity, 81 babies in 1,005 deliveries, was 8.1 per cent and for 1,030 births 7.9 per cent. The incidence of prematurity, 80 live premature babies in 1,024 live births, was 7.8 per cent. The incidence of prematurity, 62 live single premature births in 976 live single births, was 6.4 per cent. These figures are comparable to those for the entire St. Anne's population (Table I).

The deletion of the small number of 19 incomplete records would not appear to be significant. All of the premature infants and twins and half of the stillborn infants are in the group with complete records. The subsequent analyses will deal only with the 1,005 complete mothers' records and their 1,030 babies. Five of these mothers were delivered of a total of 6 stillborn infants (this includes one set of twins). Therefore, the majority of the analyses are concerned with the remaining 1,000 mothers who were delivered of 1,024 liveborn babies.

In this analysis no statistically significant differences at the 5 per cent level of confidence could be established in any category in a comparison of the premature and fullterm deliveries. Some definite trends are indicated and the data do characterize the population under study.

The majority of the mothers (Table IV and Fig. 1) were somewhat younger than the age reported for the general population of mothers in the United States.17 Thirtynine per cent of the mothers were less than 20 years of age and 73 per cent than 25. Only 12 per cent of the mothers were over 30 years of age.

The incidence of prematurity (Table V) appears to be lowest for the mothers in the

Table IV. Distribution of mothers' ages

St. Anne's Maternity Hospital			Birth rate per 1,000 female population in the United States 18		
Age (years)	No.	%	1949	1952	
Less than 15	.41	4.1	1.0	0.9	
15 - 19	355	35.3	83.4	85.4	
20 - 24	341	33.8	200.1	218.1	
25 - 29	146	14.6	165.4	180.4	
30 - 34	87	8.7	102.1	113.1	
35 - 39	26	2.6	53.5	56.1	
40 - 44	9	0.9	15.3	15.1	
45 or older	0		1.3	1.3	
Total	1,005*	100			

^{*}Includes mothers of stillborn infants.

20 to 24 year age group and highest for the mothers over 30. The younger mothers did not show any great increase in prematurity.

The marital status of the mothers (Table VI) at the time of their illegitimate pregnancies does not seem to be significantly related to the incidence of liveborn premature births. Since 84 per cent of the mothers were single and the other groups are relatively small, no conclusions can be made from this

The incidence of prematurity appears to be greater among the primiparous mothers; however, multiparous mothers made up only 18 per cent of the mothers delivered and accounted for only 12 per cent or 15 per cent of all the premature infants (Table VII).

"Racial" grouping of white-not Mexican and white-Mexican did not reveal any relationship to the incidence of prematurity (Table VIII). The group white-Mexicans are really Mexican Americans who represent a fair portion of the Los Angeles population. They constituted 21.8 per cent of the mothers in this study with 72.4 per cent of the mothers in the white-not Mexican group and only 4.1 per cent in the Negro group. This is in contrast to other studies in this country in which a large number of the mothers have been Negroes. Negroes have repeatedly been reported to have a high incidence of prematurity and, therefore, those studies that include a high incidence of Negro mothers will give different results.

Table V. Incidence of premature live births in relation to mothers' ages

Mothers' ages	Mothers delivered		Premature live births		Total No.	Incidence of prematurity for each age group*
(years)	No.	%	No.	%	live births	(%)
Less than 15	40	4.0	3	3.8	41	7.3
15 - 19	355	35.5	28	35.0	362	7.7
20 - 24	339	33.9	23	28.8	343	6.7
25 - 29	145	14.5	11	13.8	149	7.4
30 - 34	86	8.6	12	15.0	93	12.9
35 - 39	26	2.6	3	3.8	26	11.5
40 - 44	9	0.9	0	0	10	0
45 or older	0	0	0	0	0	0
Total	1,000†	100	80	100	1,024	

*There is no significant difference in the incidence of prematurity between any age levels at the 5 per cent level or less, as calculated by the Chi-square method.

†Included only mothers of liveborn babies.

Table VI. Marital status of mother at time of illegitimate pregnancy in relation to incidence of live premature births

	Mothers Premature delivered live births Total No.			Total No.	Incidence o	
Marital status	No.	%	No.	%	live births	(%)
Single	840	84.0	69	86.2	861	8.0
Divorced	101	10.1	7	8.8	102	6.9
Married	27	2.7	3	3.8	28	10.7
Widowed	17	1.7	1	1.2	18	5.6
Separated	15	1.5	0		15	0
Total	1,000	100	80	100	1,024	

*There is no significant difference between any of these categories at the 5 per cent level.

The educational level of the mothers did not affect the incidence of prematurity in this study (Table IX). The majority of the mothers, 71 per cent, had some high school education and no more, while 14.4 per cent had only grammar school education and 14 per cent had college education. There was some relationship between the age of the mother and the amount of education she received. Obviously the younger mothers would not have any opportunity to attend college (Table X). However, only 21 per cent of the mothers with only a grade school education were under 15 years of age and 52 per cent of these mothers were over 20. Similarly, 42 per cent of the mothers with just a high school education were under 20 years of age and 58 per cent were older. On the other hand, 19 per cent of the mothers with a college education were less than 20. Between the ages of 20 and 35 the distribution of approximately 10 per cent grade school education, 71 per cent high school education, and 19 per cent college education remained fairly constant. Thus, the age was not the dominant limiting factor in the amount of education the mother received, except for those less than 15 years of age. The fact that 71 per cent of the mothers had some high school education and 14 per cent had some college education may indicate that there is a selection factor in the type of girls who are delivered at the St. Anne's Maternity Hospital. Perhaps girls of a somewhat higher intelligence, educational level, and social class seek out this hospital as compared with the majority of unwed mothers.

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It had been anticipated that the incidence of prematurity would be significantly lower among those mothers who spent their last trimester or a significant portion of it at St. Anne's Hospital. It was assumed that the careful supervision received there would be beneficial. The figures (Table XI) tend to confirm this but the statistical significance of the difference cannot be established at the 5 per cent level. It is interesting that 45.6 per cent of the mothers spent their last trimester at St. Anne's Maternity Hospital and 17.5 per cent were in their own homes, while 36.6 per cent were elsewhere.

The economic status of the mother as reflected by the amount she was able to pay to defray the cost of her hospital and medical care was determined and correlated with the incidence of prematurity (Table XII). The incidence of prematurity of 6.3 per cent for "full pay" mothers, 7.3 per cent for "part pay," and 9.8 per cent for charity mothers is suggestive.

The early onset of prenatal care at St.

Anne's Maternity Hospital was assumed to be related to good prenatal supervision and hence to a reduction in the incidence of prematurity. This could not be established intrinsically in the data obtained in this study (Table XIII). The incidence of prematurity for those mothers who started care in the first trimester was 9.8 per cent, in the second trimester 5.8 per cent, in the third trimester 8.2 per cent, and none 16.1 per cent. Despite the size of the last percentage figure, there was no statistical difference between these categories at the 5 per cent level. It is important to note that 35.6 per cent of the mothers started their prenatal care at the St. Anne's Maternity Hospital in the first or second trimester and only 3.1 per cent received no prenatal care before delivery. Furthermore, many of the mothers who started their care at St. Anne's Maternity Hospital in the third trimester had been receiving prenatal care elsewhere previously. This number could not be determined accurately for this study. Thus, most

Table VII. Parity of pregnancy in relationship to incidence of liveborn premature infants

	mo	Number of mothers delivered				Incidence of
Parity	No. % No. %	live births	(%)			
Primipara	815	81.5	67	83.8	835	8.0
Multipara	183	18.3	12	15.0	187	6.4
Unknown	2	0.2	1	1.2	2	
Total	1,000	100	80	100	1,024	

*There is no significant difference between these two categories at the 5 per cent level.

Table VIII. Mothers' "race" and incidence of live premature births

Race of mother	Mothers delivered			nature births	Total No.	Incidence of prematurity*
	No.	13 %	No.	%	live births	(%)
White-not Mexican	724	72.4	60	75.0	744	8.1
White—Mexican	218	21.8	16	20.0	222	7.2
Negro	41	4.1	3	3.8	41	7.3
Other	17	1.7	1	1.2	17	5.9
Total	-1,000	100	80	100	1,024	

*There is no significant difference at the 5 per cent level.

Table IX. Education of mother and incidence of prematurity

Education of mother	Mothers delivered			nature births	Total No.	Incidence of prematurity*
	No.	%	No.	1 %	live births	(%)
Grade school only	144	14.4	8	10.0	148	5.4
High school	710	71.0	60	75.0	725	8.3
College	140	14.0	11	13.8	145	7.6
Unknown	6	0.6	1	1.2	6	
Total	1,000	100	80	100	1,024	

^{*}There is no statistical difference between these categories at the 5 per cent level.

Table X. Education of mother in relation to age

Mother's	Grade	school	High	school	Col	llege		Total
age	No.	%	No.	%	No.	%	Unknown	
Less than 15	30	20.8	10	1.4	0	0	0	40
15-19	29	27.1	288	40.6	27	19.3	1	335
20-24	35	24.3	240	33.8	61	43.6	3	339
25-29	21	14.6	94	13.2	28	20.0	2	145
30-34	9	6.2	61	8.6	16	11.4	0	86
35-39	5	3.5	14	2.0	7	5.0	0	26
40-44	5	3.5	3	0.4	1	0.7	0	9
45 or older	0		0		0	~		0
Total	144	100	710	100	140	100	6	1,000

Table XI. Mothers' place of residence during last trimester of pregnancy as related to incidence of liveborn premature infants

Residence of	Mothers delivered		Premature live births		Total No.	Incidence of
mother	No.	%	No.	%	live births	(%)
St. Anne's Maternity						
Hospital	456	45.6	31	38.8	181	6.7
Own home	175	17.5	16	20.0	463	8.8
Other	366	36.6	33	41.2	377	8.8
Unknown	3	0.3	0		3	
Total	1,000	100	80	100	1,024	

^{*}There is no significant difference at the 5 per cent level between these categories.

Table XII. Economic status of mother in relationship to incidence of prematurity

Economic status of mother	Mothers delivered		Premature live births		Total No.	Incidence of prematurity*
	No.	%	No.	%	live births	(%)
High (full pay)	63	6.3	4	5.0	63	6.3
Average (part pay)	770	77.0	58	72.5	793	7.3
Charity (no charge)	162	16.0	16	20.0	163	9.8
Unknown	5	0.5	2	2.5	5	
Total	1,000	100	80	100	1,024	

^{*}There is no significant difference at the 5 per cent level between these categories.

	Mothers delivered			nature births	Total No.	Incidence of prematurity*
Onset of care	No.	%	No.	%	live births	(%)
First trimester	57	5.7	6	7.5	61	9.8
Second trimester	299	29.9	18	22.5	310	5.8
Third trimester	612	61.2	51	63.8	621	8.2
No care	31	3.1	5	6.2	31	16.1
Total	1,000	100	80	100	1,024	

*There is no significant difference at the 5 per cent level of any of these categories.

Table XIV. Age of mother in relation to onset of prenatal care at St. Anne's Maternity Hospital

Onset of	Less t	Less than 15 1		to 19	20	to 24	25	to 29	30	to 34	35	35 to 39	40	to 44
prenatal care	No.	%	No.	%	No.	%	No.	%	No.	%	No	1 %	No.	1 %
First tri-														
mester	1	2.5	15	4.2	20	5.9	- 11	7.6	6	7.0	2	7.7	2	22.2
Second tri-														
mester	13		124	34.9	93	27.4	33	22.8	27	31.4	7	26.9	2	22.2
Third tri-														
mester	24	60.0	205	57.7	214	63.1	94	64.8	53	61.6	17	65.4	5	55.6
None	32	5.0	11	3.1	11	3.2	7	4.8	0	0	0	0	0	0
Unknown	0	0	0	0	1	0.3	0	0	0	0	0	0	0	0
Total	40	100	355	100	339	100	145	100	86	100	26	100	9	100

Table XV. Reported complications of pregnancy and incidence of prematurity

Complications _		thers vered		nature births	Total No.	Incidence of prematurity*	
of pregnancy		live births	(%)				
None	948	94.8	73	91.2	969	7.5	
Complications	49	4.9	7	8.8	52	13.5	
Unknown	3	0.3	0	0	0		

*The difference between these two groups is not significant at the 5 per cent level.

of the mothers delivered in this hospital did receive fairly adequate prenatal care; therefore, the difference might not appear within this group but in the general control of prematurity in this hospital as compared with other hospitals. This would seem to be confirmed by the over-all average instance of prematurity found in this study (Tables I, II, and III).

It is of further interest that there was no obvious tendency for any age group to start care early or to delay care (Table XIV).

The majority, 94.8 per cent, of the mothers were reported to have uncomplicated pregnancies, and the incidence of prematurity in this group was 7.5 per cent (Table XV). The 49 mothers with complicated pregnancies had 7 premature infants, an incidence of 13.5 per cent.

The sex of the babies showed some relationship to prematurity. Girls are generally smaller than boys at birth and, therefore, will fall into the premature category more often. There were 556 male babies (54.3 per

Table XVI. Sex of baby and incidence of prematurity

Sex of baby	Total li	ve births	Premature	Incidence of prematurity*	
	No.	%	No.	%	(%)
Male	556	54.3	36	45.0	6.5
Female	468	45.7	44	55.0	9.4

*The difference between these two categories is not significant at the 5 per cent level.

Table XVII. Placement of babies on leaving hospital

	Premature infants		Term	infants	Total	
Placement	No.	%	No.	%	No.	%
Remained with						
natural mother	37	46.2	444	47.0	481	47.0
Placed in adoption	33	41.2	456	48.3	489	47.8
Other arrangement	9	11.3	23	2.4	32	3.1
Unknown	1	1.2	21	2.2	22	2.1
Total	80	100	944	100	1,024	100

Table XVIII

		Score		
Item	0	1	2	
Age	20-30	Less than 20	30 or over	
Parity	Multiparous	Primiparous		
Economic status	High (full pay)	Average (part pay)	Low (charity)	
Complications of pregnancy	None	Complicated	, , , ,	
Sex of child	Male	Female		
Onset of prenatal care	First or second tri- mester	Third trimester	None	
Residence during last trimester	St. Anne's Maternity Hospital	Own home	Other	
Mother's education	College	High school	Grade school	
Marital status of the mother	Divorced, widowed, or separated	Married	Single	

cent) and, of these, 36 were premature, an incidence of 6.5 per cent, and 468 female babies (45.7 per cent) and, of these, 44 were premature, an incidence of 9.4 per cent (Table XVI).

It is interesting that 47 per cent of the mothers kept their babies with them rather than place them for adoption and 47.8 per cent placed their babies for adoption, while 3.1 per cent made some other arrangement (Table XVII). The distribution was roughly the same for the premature infants, though a somewhat larger percentage (11.3) made other arrangements. It is not known how

many of the mothers who initially take their babies with them subsequently decided to place them for adoption.

Several factors seemed to be related to an increased or decreased incidence of prematurity in this study, despite the fact that none could be established as statistically significant because of the small number of cases. For this reason, an attempt was made to get the accumulative effect of these factors by the use of an arbitrary weighing system. The items were weighed as indicated in Table XVIII.

The lowest possible score would be 0 and

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should be related to the lowest incidence of prematurity and the highest possible score would be 15 and should be related to the highest incidence of prematurity.

The first five items have been found in other studies to be significantly related to prematurity as indicated earlier in this article, and a similar trend was present in this study. The last four items were specifically related to this study. The weighted scoring on these items was based on our postulates regarding the value of early and adequate prenatal care and its possible relationship to the mother's education, and also the emotional tension that might be present in the illegitimately pregnant woman who had never been married as compared with the women who were or had been married.

The scores of the mothers with term infants were compared with those of premature infants. This was done for all items and for the first five items and the second four items separately. The analysis was also made for single live births and for twins separately.

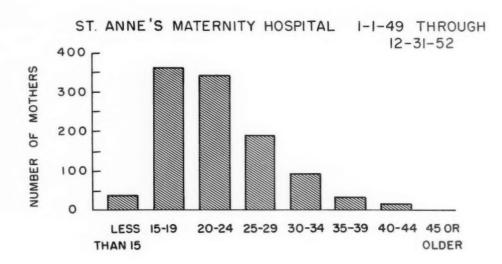
This analysis reveals (Table XIX) that the difference between the mean scores for the full-term infants and those for the premature infants is significant at the 1 per cent level as determined by the t test. Similarly, the differences in the mean scores on the first five items are significant at the 1 per cent level as determined by the t test. The last four items are not significant at a 1 or 5 per cent level of confidence as determined by the t test but are significant at a 5.1 per cent level. This suggests that these items alone can differentiate mothers of premature babies from mothers of full-term babies at a fairly high level of confidence. The mothers of twins that were term or premature infants could not be differentiated by this method.

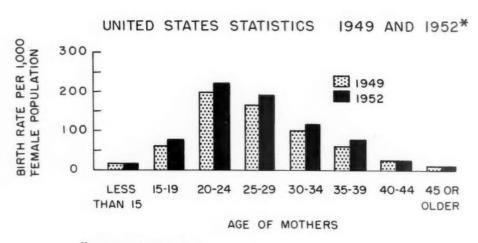
The data reported here, therefore, confirm the significance of the first five items in the scoring list as related to prematurity in the manner indicated: namely, that multiparous mothers between 20 and 30 years of age, of good economic status, with no complications of pregnancy, and bearing a male child, are the least likely to have a

Table XIX. Weighted analysis of seven items related to prematurity tested by the t test

		Single liveborn infants	All liveborn infants
All items			
Term	Mean score	7.309	7.322
	Variance	2.925	2.940
Premature	Mean score	8.00	7.923
	Variance	2.552	2.513
	Value of t*	3.207 P = 0.0007	3.199 P = 0.0007
First five items (age,	, parity, economic status, o	complications of pregnancy, sex	of baby)
Term	Mean score	3.030	3.042
	Variance	1.154	1.138
Premature	Mean score	3.458	3.423
	Variance	1.390	1.416
	Value of t	2.710 P = 0.0034	2.818 P = 0.0025
Last four items (onse	et of prenatal care, residence	e during third trimester, mothe	rs' education, marital status
Term	Mean score	4.279	4.282
	Variance	1.741	1.759
Premature	Mean score	4.542	4.500
	Variance	1.425	1.292
	- Value of t	1.632 P = 0.0514	1.605 P = 0.0543

^{*}A value of t of 2.362 = P < 0.01; a value of t of 1.645 = P < 0.05.





* REFERENCE NO. 8

Fig. 1. Distribution of mothers' ages graphically illustrated.

premature infant. On the other hand, primiparous mothers over 30 or under 20, of lower economic status, with complications of pregnancy, and bearing a female child, are most likely to have a premature infant.

Likewise, the original hypothesis could be established at a fairly high level of confidence that early prenatal care, residence at St. Anne's, the higher education of the mother, or marital status of the mother might be related to a decreased incidence of prematurity. It is further possible that the entire population at St. Anne's Maternity Hospital is different in terms of receiving

better prenatal care than the total population of illegitimately pregnant women, reducing somewhat the value of these items in the evaluation of this particular population.

Comment

The incidence of premature births is the same for the illegitimately pregnant women at St. Anne's Maternity Hospital as it is for the general population in this area and as reported for the nation. This is in contrast with the many reports of a much higher incidence of prematurity for illegitimate pregnancies.¹⁻⁸

There are several plausible reasons why the incidence of prematurity might be greater in illegitimate pregnancies. These pregnancies are generally primiparous and in younger women of lower socioeconomic background. All three of these factors have been established as related to prematurity.2-4, 10, 13 Primiparous and the youth of the mothers were factors operating in the population at St. Anne's Maternity Hospital without apparently significantly increasing the incidence of prematurity. Unfortunately, the socioeconomic status of the women at St. Anne's Maternity Hospital was not determined in such a way that this population could be compared with another group of unmarried mothers.

It is sometimes assumed that the lower socioeconomic status of the unmarried mother as well as the illegitimate pregnancy may deter her from receiving adequate prenatal care. This lack of prenatal care may be the dominant factor in the generally reported increased incidence of prematurity in illegitimate pregnancies. Toverud7 demonstrated that improved nutrition reduced the incidence of prematurity in a group of unmarried mothers. The maternity study in Great Britain² established the benefits of adequate prenatal care for prevention of prematurity among all pregnant women. It was not possible to demonstrate definitely the benefits of early prenatal care in this study because of the small numbers of patients. It is possible that the great majority of the mothers delivered at St. Anne's received more adequate prenatal care and closer supervision in the last trimester than the general population of illegitimately pregnant women and as good as that of the general population of married mothers. This could account for the relatively "normal" incidence of prematurity at St. Anne's Maternity Hospital.

It is interesting that contrary to most other studies Drillien8 did not find an increased incidence of prematurity in young mothers, particularly in those under 20 years of age. She also found that the younger mothers had fewer complications of preg-

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nancy. She determined that on the basis of their younger age, illegitimately pregnant mothers, as a group, should have fewer premature births than the general population. She concluded that "the excess . . . of prematures among the unmarried mothers must be due to causes other than age or complications."

Douglas,18 who has found that mothers under 20 years of age do have a higher incidence of prematurity, feels that Drillien was dealing with a selected hospital sample who received special attention. He indicates that adequate prenatal care and adequate rest in the last trimester are very important factors in preventing premature birth.

From available information it seems most likely that illegitimately pregnant women have a greater risk of premature labor than the general population because of their youth, primiparity, and inadequate prenatal care. Since the first two factors cannot be altered, attention should be focused on providing these mothers adequate care throughout their pregnancies.

Summary

Numerous reports have indicated that the incidence of prematurity is significantly higher in illegitimate pregnancies than in the general population of pregnant women. This has been attributed to the primiparity and youth of the mothers, a generally low socioeconomic status, and inadequate prenatal care.

The incidence of prematurity at the St. Anne's Maternity Hospital for unmarried mothers in Los Angeles was found to be 7.7 per cent for 1,034 live births in the period Jan. 1, 1949, through Dec. 31, 1952. This is comparable to a reported incidence of 7.4 per cent for the nation, 6.9 per cent for California, and 7.7 per cent for Los Angeles in approximately the same time period. It would appear that in this particular situation there is no increase in the incidence of prematurity in illegitimate pregnancy.

By comparing detailed data on the mothers of full-term infants and those of premature infants delivered at St. Anne's Maternity Hospital, an attempt was made to determine the predisposing factors to prematurity. No single factors could be isolated with statistical significance, presumably because of the small size of the sample. By combining several factors with an arbitrary weighting system it was possible to differentiate the mothers of full-term babies from the mothers of premature babies. The multiparous mother between 20 and 30 years of age with no complications of pregnancy, of a high economic status, and bearing a male child was least likely to be delivered prematurely. The benefits of early prenatal care or careful supervision in the last trimester could not be definitely established in this population.

It is thought possible that the majority of the mothers at the St. Anne's Maternity Hospital get better prenatal care than the general population of unmarried mothers and care equal to that of the general population of married mothers. This might account for the "normal" incidence of prematurity in this hospital.

Illegitimate pregnancy per se does not predispose to prematurity. Adequate prenatal care should be as effective in preventing prematurity with these mothers as it is in the general population.

I wish to acknowledge the considerable help given me by the Sisters of St. Anne's Maternity Hospital. Mrs. B. J. Fitzpatrick, a volunteer helper in the hospital, did the major share of the data recording. Miss Barbara Hanley of the Division of Biostatistics aided in the statistical analysis.

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GYNECOLOGY

Laboratory and clinical effects of nortestosterone

II. The endometrial response

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Boston, Massachusetts

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THE availability of synthetic steroids with potent oral progestational activity has provided gynecologists with a valuable therapeutic tool. In a previous report¹ experience with small doses of nortestosterone in the management of anovulatory dysfunctional uterine bleeding was described.

In addition, the use of these agents has been suggested in the prevention of ovulation^{2, 3} and in the treatment of endometriosis,⁴ threatened abortion,⁵ amenorrhea, and infertility associated with progestational deficiency.^{3, 6}

The results with the use of 17-alpha-19-nortestosterone (norethindrone) in the treatment of progestational deficiency have been equivocal. Cohen⁶ has reported on the treatment in 12 patients in 23 cycles; no pregnancies occurred. Tyler,³ on the other hand, reported 19 pregnancies when the same agent was used in 75 cases. The dosage described by both these workers was 10 mg. of norethindrone daily, starting 2 or 3 days after ovulation.

The selection of this dosage level for sup-

portive therapy of the endometrium is apparently empirical. It has been shown that norethindrone is capable of converting a proliferative endometrium to a secretory one, but a study of the effect of varying dosages and varying durations of administration has not been reported.

Rock⁷ and others have described the effect of 10 to 40 mg. of norethindrone, as well as other steroids, on the endometrium given over a 15 to 20 day period, but no attempt was made to relate the time of biopsies to the observed effect, nor were smaller dosages utilized.

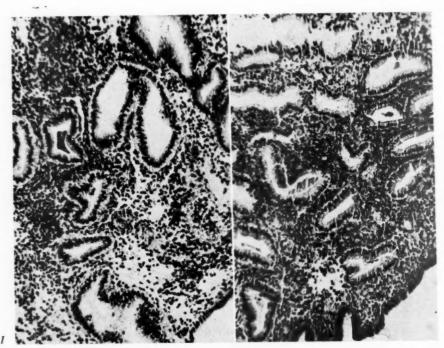
It was felt that an investigation of the effect on the endometrium of smaller dosages of these steroids, observed at varying and controlled time intervals, would help throw light on the progression of endometrial changes and in this way provide a more rational basis for therapeutic application.

Material and methods

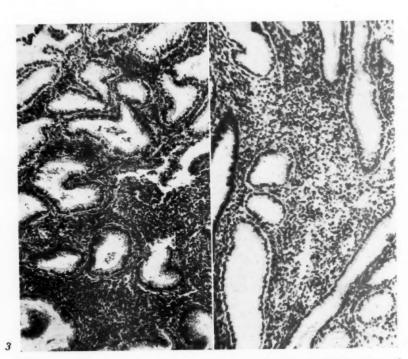
Clinic and private patients with varying menstrual disorders were utilized for the study. These patients had been receiving medication as part of therapy, and they had volunteered to undergo endometrial biopsy. Seven subjects were known to have infrequent and irregular cycles associated with anovulation. Two patients, aged 35 and 39,

From the Surgical Service (Gynecology) of the Peter Bent Brigham Hospital and the Department of Gynecology, Harvard Medical School.

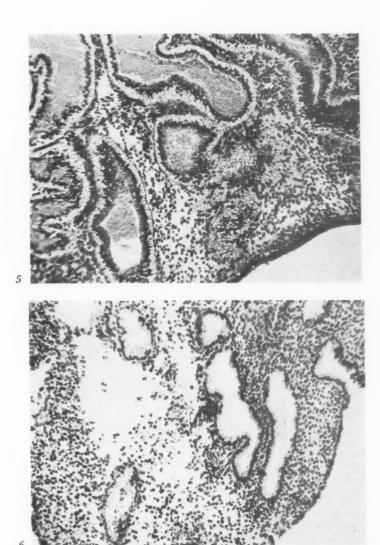
This study was supported by a grant from the Population Council.



Figs. 1 and 2. Endometrial biopsies on seventh day of administration of 2.5 mg. norethindrone daily. Subnuclear vacuolization is prominent. Stromal edema is variable.



Figs. 3 and 4. Endometrial biopsies on seventh day of administration of 5.0 mg. norethindrone daily. Both subnuclear and supranuclear vacuoles are present. Stromal edema is variable.



Figs. 5 and 6. Endometrial biopsies on seventh day of administration of 10 mg. norethindrone daily. Both subnuclear and supranuclear vacuoles are present. Edema is prominent. No predecidua.

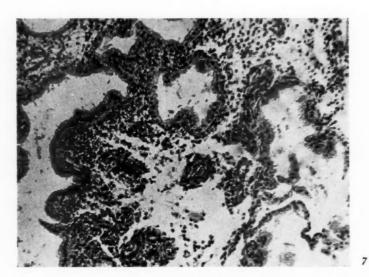
were suffering from premature menopause and had been on replacement estrogen therapy since the diagnosis had been made.

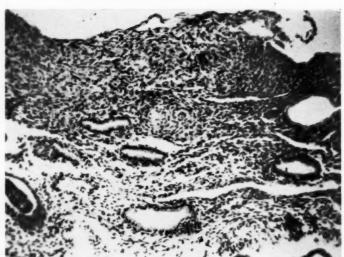
In the patients producing their own estrogen, treatment was begun in the proliferative phase as determined by an examination of the basal body temperature chart and cervical mucus. If the cervical mucus showed excellent ferning, it was assumed that the patient was producing sufficient estrogen to prime the endometrium, and treatment with nortestosterone was begun at that time. In patients who were still anovulatory according to the basal body temperature chart but in whom there was evi-

dence of insufficient estrogen as demonstrated by poor ferning of the cervical mucus, 2 mg. of diethylstilbestrol was administered daily for 14 days before nortestosterone was started. The estrogen intake was continued along with the nortestosterone.

The effects of norethindrone* on the primed endometrium at 2.5, 5, and 10 mg. doses given over 7 and 14 day periods, respectively, were studied. Endometrial biopsy specimens were obtained on the seventh and

^{*}Norethindrone was supplied as Norlutin by Dr. J. E. Gajewski of Parke, Davis & Company.





Figs. 7 and 8. Endometrial biopsies on the fourteenth day of administration of 2.5 mg, norethindrone daily. Glands show secretory exhaustion. Early predecidua is noted in the stroma.

fourteenth days of norethindrone administration. An example of 2 cases was studied at each dose and time level. Pregnanediol determinations were performed on the urine on the day of biopsy to rule out an intrinsic source of progesterone. In all cases the pregnanediol values were reported as negative

The endometrial biopsies were read and the findings were then correlated with the dosage level.

Results

Figs. 1 through 6 demonstrate the results of short-term administration of norethin-

drone. Figs. 1 and 2 demonstrate the effect of 2.5 mg. given daily for 7 days. In Fig. 1 there is basal vacuolization in the glands and edema of the stroma suggestive of early secretory endometrium. Yet this is atypical in that the glands are not dilated and the edema is out of proportion to the changes in the glands. In Fig. 2, at the same dosage level, the glands seem more advanced with many supranuclear vacuoles. On the other hand, the stroma is less advanced; it resembles proliferative stroma.

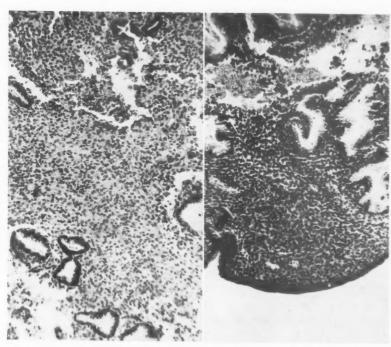
Increasing the dosage to 5 mg. daily fo 7 days (Figs. 3 and 4) apparently produce little progression in the glands. There is still

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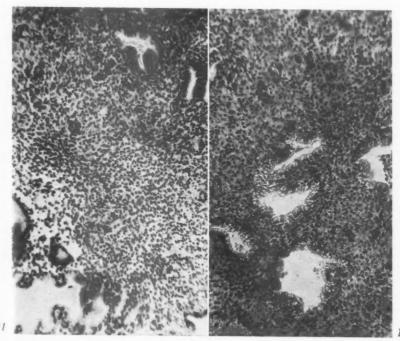
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Figs. 9 and 10. Endometrial biopsies on the fourteenth day of administration of 5 mg. norethindrone daily. Glands vary from late secretory effect to secretory exhaustion. Predecidua is prominent in Fig. 9 and less so in Fig. 10.



Figs. 11 and 12. Endometrial biopsies on the fourteenth day of administration of 10 mg. norethindrone daily. Glands vary from late secretory effect to secretory exhaustion. Stroma shows marked predecidua.

both subnuclear and supranuclear vacuolization. The stroma is variable. In one case (Fig. 3) it is suggestive of proliferative stroma, while in the other (Fig. 4) edema is prominent.

Increasing the dosage still further to 10 mg. daily for 7 days, as shown in Fig. 5, brings about little progression of activity in the glands. There is a persistence of subnuclear vacuoles. There is slight edema of the stroma and no predecidua formation. The profuse secretion in the lumen is atypical for glands with subnuclear vacuoles. In a parallel case (Fig. 6), however, the glands appear more advanced with chiefly supranuclear vacuoles. The stroma also shows slight edema and no predecidua.

Figs. 7 through 12 depict the changes noted when the same three dosage levels were given over a 2 week period.

In both Figs. 7 and 8, in which 2.5 mg. of norethindrone was administered daily for 14 days, the glands show secretory exhaustion, typical of later stages of secretory activity. In Fig. 7 there is early predecidual reaction, but this is atypical in that islands of predecidual cells are separated by edema. A tendency to predecidua formation along with slight edema is also shown in Fig. 8.

With 5 mg. of norethindrone given for 14 days (Figs. 9 and 10) the glands are similarly at a late stage of secretory activity. In Fig. 9 there is marked predecidual reaction, and the leukocyte infiltration is suggestive of early menstrual endometrium. The stroma in Fig. 10 shows less wellformed predecidua, and the glands are still quite active.

Endometrial biopsies after 10 mg. daily for 2 weeks (Figs. 11 and 12) once again show glands that demonstrate secretory exhaustion. There is marked predecidual reaction, but the slight edema in Fig. 11 is atypical, as is the active secretion noted in some of the glands of Fig. 12.

Comment

In interpreting the results one must first make note of the variability that is often present between the two observations at each dose level. This may be due to the variation in individual absorption and utilization of the hormone; it may be due to the variation in endometria coming from patients with different clinical entities; or it may be due to the error in sampling as represented by one endometrial biopsy.

In addition, atypicality in relation to the normal endometrial development is also a consistent finding. The endometrial pictures for the most part do not coincide with those of any typical, naturally occurring secretory endometrium at definite ages. Very often there is a divergence of effect with rapid development in the glands without a similar effect in the stroma.

Within the framework of the above observations, however, a rough pattern can be noted. It appears that merely increasing the dosage over a short period of time has little effect in ripening the endometrium. The endometrium under the influence of progestational stimulation requires time for maturation. As would be expected, a 2 week interval seems optimum.

In addition, it appears that a dose of between 5 and 10 mg. daily, given over a 14 day period, can most closely simulate the action of intrinsic progesterone in the normal menstrual cycle. It is possible that a dosage higher than this, by distorting the endometrial pattern, would be of little value in replacement therapy.

In supplemental therapy, as in the treatment of progestational deficiency, it is possible that 2.5 or 5 mg. of extrinsic hormone added to the intrinsic supply would suffice. Higher degrees of progestational activity could possibly stimulate the endometrium beyond the phase optimum for implantation and hinder rather than aid this process.

Summary

Twelve endometrial biopsies in 9 patients who were receiving varying dosages of nortestosterone were carried out.

Biopsy specimens were taken after the administration of 2.5, 5, and 10 mg. daily for 5 and 7 days, respectively.

On the basis of the observations in this

study, it appears that the optimum replacement dose of norethindrone lies between 5 and 10 mg. daily over a 14 day period.

The optimum supplemental dose seems to lie between 2.5 and 5 mg. daily for 14 days.

I am indebted to Dr. Donald G. McKay for reviewing the pathologic material.

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Management of endometriosis with nor-progesterone

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THIS is a report of 112 cases of endometriosis managed with newer progestational therapy. Sixty of the patients were proved to have endometriosis prior to therapy by previous laparotomy, culdoscopy, or culpotomy.

That nor-progesterone substances are capable of producing decidual changes in ectopic endometrium has been reported previously.^{1, 2} That pregnancy can produce decidual changes in ectopic endometrium has also been reported, as long ago as 1911.³

The purpose of this paper is to report on results obtained in management of endometriosis with norprogesterone, pointing out certain microscopic features and relating experiences, both bad and good, which were encountered during the study.

Material and methods

Patients included in this study were seen in the Outpatient Department of the National Naval Medical Center, Bethesda, Maryland, and the Gynecologic Section of the Main Navy Dispensary, Washington, D. C. All patients sought medical care because of one or more of the following symptoms: dyspareunia, dysmenorrhea, menorrhagia, infertility, or painful defecation at or near the menses. Any patient who was symptomatic, who had a previous history of operatively proved endometriosis, and who at this time had clinical evidence of recurrent disease, was considered for the study. Twenty patients fell into this group. Any patient who was symptomatic and who on pelvic examination was considered to have endometriosis was admitted to the hospital for colpotomy or culdoscopic confirmation of the diagnosis. Forty patients were in this category. After the study was well under way, any patient who was symptomatic and who on pelvic examination was felt to have endometriosis was examined by other staff members and, if the findings of all were in agreement, the patient was started on hormonal therapy. This group comprised 52

When a patient was considered to be in one of the aforementioned categories norprogesterone therapy was started. The outpatient record was tagged and all prescriptions for nor-progesterone were held out at the pharmacy for a double check. The patient was seen monthly throughout the course of treatment by the same physician and, after treatment, every 3 months for as long as it was feasible. This follow-up period varied from 6 to 30 months. Endometrial biopsies were done in the early part of the study on all patients, but later only in cases which were to be managed operatively.

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This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

Presented at the annual Armed Forces Obstetrics and Gynecology Seminar, U. S. Naval Hospital, Portsmouth, Virginia, Oct. 26-29, 1959. t

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Two progestins were utilized, norethindrone* and norethynodrel.†

After the study had been well under way, it was felt that although norethindrone produced less nausea and vomiting it was associated with more acne, more fluid retention, and more often with troublesome breakthrough bleeding. In view of this, norethynodrel was then used as the only medication. Dosage of both drugs consisted of 10 mg. daily for 2 weeks, then 20 mg. daily for 2 weeks, then 30 mg. daily for 8 months. In the event that breakthrough bleeding occurred, the dosage was increased 10 mg. daily until the bleeding was controlled. At no time did daily dosage exceed 60 mg.

Any patient who after treatment was found to complain of the same symptoms as before treatment was subjected to operative management, regardless of the posttreatment pelvic findings. These patients have been separated into two groups, (a) symptomatic with operatively proved disease, (b) symptomatic without evidence of operatively proved disease.

Side effects and complications were noted on the outpatient records; these were tabulated at the end of the study.

Morphologic-anatomic findings

Most of the material examined consisted of biopsy specimens of endometrium obtained at various times during the course of nor-progesterone therapy but also included were biopsy specimens of ectopic endometrium from the uterus, ovaries, and peritoneum. It was noted that the volume of the intrauterine endometrium available from biopsies decreased with increasing periods of treatment.

Microscopic examination was carried out on routine paraffin sections stained with hematoxylin and eosin. The changes seen fall into two categories-stromal and glandu-

In the stroma, cytoplasmic swelling of the stromal cells is evident as early as 3 weeks. The cytoplasm stains lightly basophilic, has distinct polygonal borders, and is homogeneous in appearance so that the cells resemble very closely those of the decidua of pregnancy. As therapy progresses, the cell matrix begins to show edema and focal infiltrates of mononuclear inflammatory cells and neutrophils (Fig. 1). The cells undergo cloudy swelling and hydropic degeneration and the nuclei become somewhat eccentric in position (Fig. 2). Later in treatment, focal areas of cellular degeneration appear with disintegration of the cytoplasm and an increase in the inflammatory cell infiltrate (Figs. 3 and 4). A biopsy specimen taken after 7 months of therapy is illustrated in Fig. 5. The stroma is edematous, the cells exhibit only fibrillary strands of cytoplasm, and they are reduced in numbers. Plasma cells and mononuclear inflammatory cells are found in larger aggregates.

Glandular changes, while less consistent than stromal changes, resemble those of the stratum compactum of decidua. Progressive dilatation with flattening of the epithelium and decrease in glandular elements is the usual result of nor-progesterone therapy (Figs. 1 and 3). In some cases the epithelium becomes flattened and the gland resembles an endothelium-lined space. On the other hand the glands retain proliferative appearance in a few cases (Fig. 5).

Ectopic endometrial implants undergo like changes with nor-progesterone as illustrated in sections from ovarian and peritoneal implants (Figs. 6, 7, and 8). The edematous stroma with its swollen polygonal cells is similar in appearance to the endometrium described above.

The available material allows no definitive conclusions regarding final morphologic changes in endometrial implants of patients treated with nor-progesterone. However, the following provocative case is cited. Fig. 9 illustrates a pretreatment biopsy of a rectovaginal septum endometrioma. This patient received 9 months of therapy with norethynodrel. Following treatment the patient con-

^{*}Norlutin, brand of norethindrone, Parke, Davis & Company.

[†]Enovid, brand of norethynodrel, made available through G. D. Searle & Company,

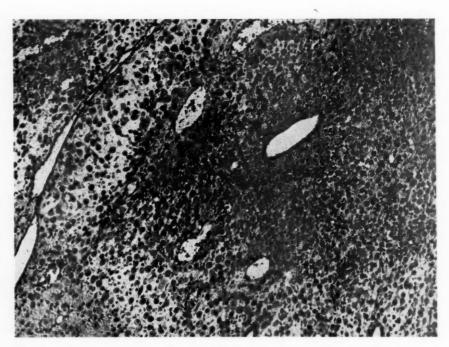


Fig. 1. Endometrium after 3 weeks of nor-progesterone therapy. The decidual stroma is edematous and is infiltrated by inflammatory cells. Glands are dilated and sparse. (Original magnification $\times 60$.)

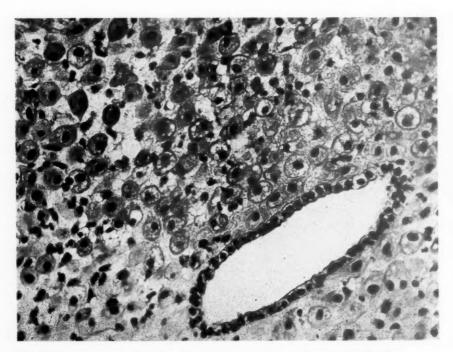


Fig. 2. Endometrium after 3 weeks of nor-progesterone therapy. Hydropic degeneration of stromal cells and a scattered mononuclear and neutrophilic infiltrate are well illustrated. (×200; reduced 1/10.)



Fig. 3. Endometrium after 3 months of nor-progesterone therapy. There is an increase in inflammatory cells and marked flattening of glandular epithelium. ($\times 60$; reduced 1/10.)

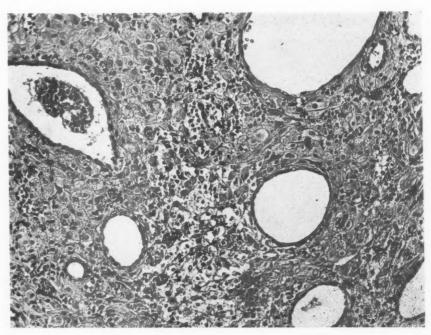


Fig. 4. Endometrium after 6 weeks of nor-progesterone therapy. There is focal degeneration and the inflammatory cell infiltrate is more prominent. ($\times 100$; reduced 1/10.)

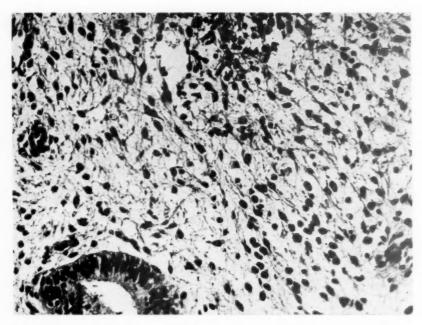


Fig. 5. Endometrium after 7 months of nor-progesterone therapy. Stromal cells reduced in number; cytoplasm scanty; chronic inflammatory cell infiltrate, while focal, is more prominent.

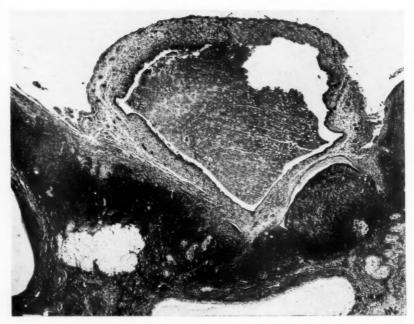


Fig. 6. Endometrial implant of ovary illustrating deciduoid appearance of stroma after nor-progesterone therapy. ($\times 10$; reduced 1/10.)

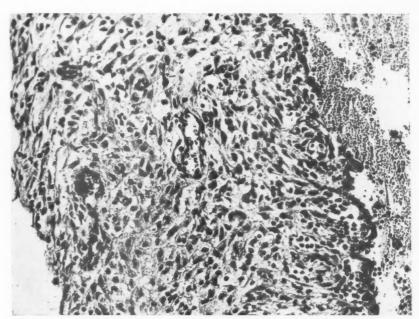


Fig. 7. Endometrial implant shown in Fig. 8 magnified to illustrate early degeneration changes in the deciduoid stroma.

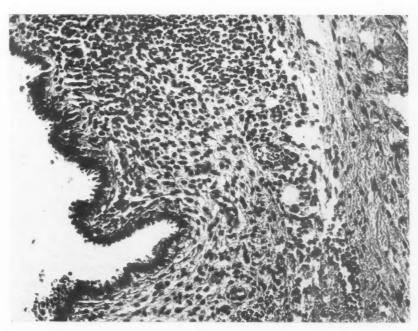


Fig. 8. Peritoneal endometrial implant with deciduoid stromal change after nor-progesterone therapy. ($\times 100$; reduced 1/10.)

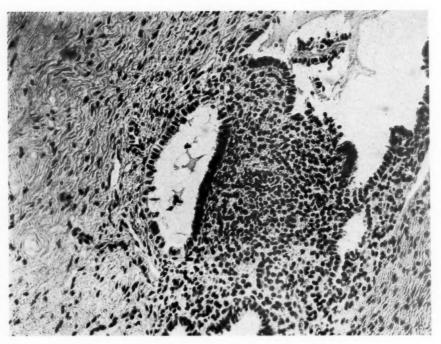


Fig. 9. Endometrioma from rectovaginal septum. (×100; reduced 1/10.)

tinued to complain of painful defecation, and operative management was carried out. Except for filmy adhesions and some fibrosis, no gross evidence of active endometriosis was found. Careful examination of the surgical specimen revealed no evidence of residual endometriosis.

Clinical results

Table I depicts the total number of cases of endometriosis seen from July 1, 1957, to July 1, 1959. Included in this total are 40 patients operated on for endometriosis but they are not included in the nor-progesterone study. Twenty-seven of these 40 were managed by total hysterectomy and bilateral salpingo-oophorectomy and 13 by so-called "conservative management." The latter group has been placed on nor-progesterone postoperatively as adjunctive therapy; no results are available concerning these cases. As described in "Material and methods," culdoscopy was valuable in confirming 34 cases although colpotomy was resorted to on 6 occasions because of marked involvement of the cul-de-sac.

Table II relates the number of patients operatively proved to have endometriosis. Table III tabulates the number of cases according to the type of progestin used. Final results as to response to each drug are not tabulated, since the relatively small number of patients on norethindrone would weight any percentages as to its value. Suffice is to say, we feel this drug produced favorable response, but it was discontinued because of the earlier stated reasons. Table IV tabulates the over-all final outcome of the 112 cases. It is felt that 85 cases or 77.6 per cent can be considered as clinically and symptomatically corrected. More specifically, these patients freely state that they feel better after treatment than they have for many years. Their comments as to correction of dyspareunia were especially gratifying. We feel this symptom alone in the presence of clinically diagnosable disease more than warrants corrective therapy.

As is evident, 7 cases were considered clinically corrected, but these patients continued to have symptoms. Since this was an investigative study and since the patients

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continued with symptoms, a surgical procedure was carried out in each case. One of these has been discussed. Five cases were considered failures from all standpoints, grossly, microscopically, and symptomatically. All of these showed good decidual effect in the endometrium but endometriosis was evident grossly and microscopically in spite of prolonged therapy. We are at a loss to explain apparent variable response to norprogesterone in this 4.5 per cent of cases although Novak4 commented that variable response of ectopic endometrium has been noted before.

Table V shows the breakdown of results in operatively, culdoscopically, or colpotomy proved cases. Percentagewise, these figures compare favorably to those in Table IV, which shows results in the over-all group.

The 13 cases of failure due to the drug are further broken down in Table VI. Five patients failed to return after the first month of therapy. These must be considered as failures since they probably did not come back because of drug side reactions. In 8 cases the drug was stopped because of severity of side effects but not lack of response to corrective medication. Specifically, 2 were because of severe nausea and vomiting and 2 because of marked emotional distress. These latter patients exhibited marked depression, so much so that their home life became unbearable. Both in these cases and in the cases of emotional distress of milder degree, marked fluid retention was coincidentally present. The final cause for drug cessation was rapid growth of fibroids. This was most dramatic in all 4 cases. In 2 of these, early operation was resorted to because of associated severe pain. Both removed specimens revealed fibroids, grossly described as showing red degeneration. This is most interesting since we feel that red degeneration is most commonly seen as a complication of pregnancy. In one of these cases the patient had severe diabetes and while she was on nor-progesterone the diabetes was most difficult to control. Following cessation of norethynodrel and operation, the diabetes rapidly became manageable.

Table I. Total cases of endometriosis seen and management

Hysterectomy, bilateral salpingo-	
oophorectomy, primary	27
Conservative management, primary	13
Nor-progesterone	112
Total	152

Table II. Operatively proved cases

Culdoscopy	40
Previous laparotomy	20
Total	60

Table III. Type of progestin used

Norethindrone	20
Norethynodrel	92
Total	112

Table IV. Response in total patients treated

	No. patients	%
Clinical and symptomatic		
correction	87	77.6
Clinically corrected but		
symptomatic	7	6.3
Failure, gross, microscopic, and		
symptomatic	5	4.5
Failure because of drug	13	11.6
Total	112	100.0
	0	

Table V. Results in operatively proved cases

4	No. cases	%
Good results	49	81.6
Clinically and histologically cor-		
rected but symptomatic	4	6.65
Histological failure and symptoma	tic 3	5.1
Drug stopped	4	6.65

Table VI. Failures because of drug

	No. cases	%
Nausea, severe, no response to		
treatment	2	1.8
Emotional distress, severe	2	1.8
Rapid growth of fibroids	4	3.6
Unknown (patients did not return)	5	4.5

Table VII. Side effects

	No.	%
Nausea, mild	99	79.5
Nausea, severe	2	1.8
Breast tenderness, mild	5	4.5
Emotional distress, mild	5	4.5
Emotional distress, severe	2	1.8
Rapid growth of fibroids	4	3.6
Breakthrough bleeding	43	38.7
Fluid retention	56	50.0
Unknown (5 patients did not return)	5	4.5

Table VII tabulates side effects. These are not too different from those reported by Kistner and Andrews.1, 2 By and large, nausea will disappear spontaneously after 4 to 6 weeks of therapy; however, these patients can be made comfortable by an antiemetic. As stated before, this symptom can be severe enough to cause the drug to be discontinued. Breast tenderness does occur, but in these cases it does not seem to be much of a problem. It was most disturbing when the drug was increased rapidly. Emotional distress characterized by severe depression was quite a problem and as stated previously, it caused the drug to be stopped in 2 cases. Rapid fibroid growth, when it occurred, was most dramatic and its possibility of occurrence must always be kept in mind. Breakthrough bleeding was observed but rapidly responded to dosage increase when norethynodrel was used. Control of this side effect in cases managed with norethindrone was not as satisfactory. Fluid retension usually responded to chlorothiazide, and patients were instructed to use this drug on an "as necessary" basis. As stated earlier, when emotional distress was a problem the patient always had coincident fluid retention which did not respond too well to diuretics.

Comments and conclusions

From the results obtained in this study, it is felt that certain conclusions can be

drawn. We feel that norprogesterone does effect ectopic endometrium favorably from the hosts' standpoint and can be expected to produce subjective and objective relief both during and after therapy in 75 to 80 per cent of the cases. Since long-term followup is not yet available, duration of therapy is prolonged (9 months), and troublesome side effects do occur, use of this drug for conservative management of endometriosis should at present be restricted to symptomatic patients, 35 years and younger, especially where childbearing is to be considered. Since use of this drug is relatively new and since it can affect the entire endocrine system, judicious caution should be utilized when coincident disease entities are associated. Whether the disease is eradicated as a result of decidual reaction followed by necrosis or by some other process, we are unable to tell from the microscopic sections available to us.

Summary

- 1. One hundred twelve cases of endometriosis treated with nor-progesterone are presented.
- 2. Microscopic evidence of the drug's effect on ectopic endometrium, normal endometrium, and fibroids is related.
- 3. Side effects and general comments concerning experiences with nor-progesterone are discussed.
- 4. The final modus operandi of prolonged nor-progesterone in eradicating ectopic endometrium remains unsolved.

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Endometriosis of the cervix

Classification and analysis of 17 cases

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ENDOMETRIOSIS designates that pathological process characterized by the presence of endometrial glands and/or stroma in ectopic foci, a lesion rarely encountered in the cervix. Thus, Javert2, 3 discovered only 7 cervical cases in a group of 599 patients affected with external endometriosis. The latter were screened from 24,436 gynecological admissions, an incidence of 1:3,500. Scott and TeLinde⁸ reported 13 cases among 560 patients surgically treated for external endometriosis between the years 1933 to 1947. It is worthy of note that 2 of these patients were never pregnant and thus never exposed to the cervical trauma incidental to delivery or abortion. Six had undergone previous cervical operations, while the remaining 5 had secondary forms of endometriosis resulting from spread of primary endometriosis elsewhere in the pelvis. Ranney and Chung⁷ attributed this low incidence to the following: (1) nonrecognition of the lesion because of its minute size; (2) failure to use tissue examination when cervical endometriosis was suspected; (3) obscuration of the microscopic characters of the cells resulting from the tissue trauma incurred when biopsy was employed. Williams and Richardson,9 however, recorded cervical endometriosis with much greater frequency and dis-

covered 12 patients with the disease during their routine gynecological examination of 719 consecutive admissions, a ratio of 1:160. They ascribed the greater frequency to clinical examination performed in the immediate premenstrual phase when congestive hyperemia accentuated the disease. It is obvious, however, that endometriosis concealed in the endocervix or lying somewhat more deeply beneath the squamous lining of the ectocervix or vaginal epithelium would nevertheless escape detection.

Classification and etiology

Cervical endometriosis can be divided into primary and secondary groups, either of which may be ectocervical or endocervical in position. It is conceded that a minute asymptomatic primary lesion associated with cervical endometriosis may escape recognition and thus somewhat invalidate true classification. Furthermore, while primary cervical endometriosis may occur independently or concomitantly with pelvic endometriosis, in this tabulation all such cervical lesions were classified as secondary forms. For the diagnosis of primary cervical endometriosis Lash and Rappaport⁵ have formulated the following criteria: (1) circumscription of the disease to the anterior lip of the cervix; (2) limitation of the lesion to the surface, or its presence immediately subjacent to the squamous lining of the cervix; (3) restriction of endometriotic islands to the confines of an old cervical scar; (4) ces-

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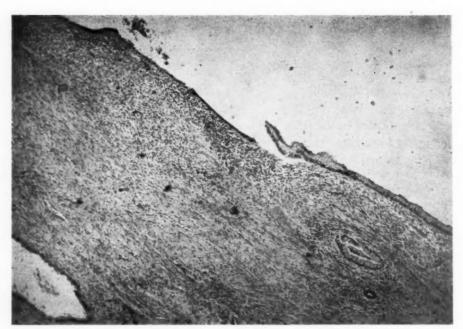


Fig. 1. (Case 5; 57-3411.) "Epithelial mutation" as cause of cervical endometriosis. On the right of the gland space, cells are endocervical and the underlying stroma is fibrillar. On the left the lining cells are endometrial and the underlying stroma comprised of round cells is of endometrial stamp. Red blood cells are irregularly distributed in this stromatogenous mantle. (×100; reduced ½.)

sation of symptoms after excision of the lesion; and (5) absence of endometriosis in the rectovaginal septum or the serosal segment of the supravaginal cervix. Ranney and Chung⁷ regarded all endometriotic lesions of the pars vaginalis of the cervix as primary in type if extension from the rectovaginal septum or serosa of the supravaginal cervix could be excluded. Lesions which involved the endocervix or in which only stromatogenous elements were present after repeated microscopic study were automatically excluded from the primary group. Secondary cervical endometriosis results from (1) a descent of corporeal stromatosis or adenomyosis interna from the corpus into the cervix; and (2) direct extension or metastatic spread of endometriosis from similar contiguous lesions occurring primarily in the rectovaginal septum, pelvic peritoneum, or ovaries.

The cause of endometriosis in the cervix, as elsewhere, is controversial. Perhaps Scott and TeLinde⁸ best summarized the situa-

tion by noting that even Sampson, "the father of the transplantation theory," ultimately conceded that no one explanation could be given for all cases. Javert2, 8 who disclaimed "serosal metaplasia" as a cause of endometriosis, invoked a composite theory of primary "endometrial transport and implantation," with propagation of the disease along lymphatic and vascular channels. For this etiological mechanism, trauma (incurred during delivery or operation) has been considered the dominant cause. The tissue defects which result from injury afford the necessary sites for the implantation and subsequent growth of detached endometrial fragments. This view is endorsed by Scott and TeLinde,8 and Lash and Rappaport.8 Furthermore, Novak and Hoge,6 after a study of 31 specimens of superficial cervical endometriosis obtained in the progestational phase, concluded that the presence of the premenstrual morphological pattern in the glands and stroma indicated such previous transport and implantation. The prolonged

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and inconstant interval between "cervical trauma and implantation," and the clinical appearance of the disease bespeaks the slow growth tempo of the implanted endometrial fragments. Indeed, a successful take must be extremely uncommon, for the low incidence of the disease is in striking contrast with the huge number of patients subjected to cervical injury. Generally, inflammation of the cervix, bacterial contamination of the vaginal field, and desquamation of the surface epithelial cells comprise effective barriers.

Primary endometriosis of the cervix and vagina also occurs in the absence of trauma. Two such cases were reported in the series of Scott and TeLinde8 and one in the collection of Williams and Richardson.9 The explanation for this group is contained in the embryogenesis of the vagina. According to Koff,4 the primary embryonal vagina is a solid plate resulting from the fusion of the terminal Müllerian tubercle with the everting sinovaginal bulbs. The former projects into the cavity of the urogenital sinus; the latter proceed from its posterior wall to engulf, fuse, and consolidate with the tubercle. Subsequent central cavitation results in the formation of the upper four fifths of the vaginal canal and its fornices. For the atraumatic group of cervical endometriosis it is herein postulated that rests derived from the central Müllerian tubercle remain locally unabsorbed or become regionally displaced to be ultimately incorporated into the walls of the upper vagina, its fornices, and the infravaginal cervix. Such primary cases of cervical and/or vaginal endometriosis may be attributed to "developmental ectopia." The factors causing activation of the rests and formation of the lesion long after the onset of the menarche are unknown. Goodall¹ clinically described such vaginal cases which appeared as velvety patches, becoming especially prominent in the premenstrual phase because of vascular congestion. In one patient the lesion was sufficiently large to involve one quarter of the surface of the entire vaginal vault. Functioning ectopic Müllerian rests displaced beneath the ectocervical or vaginal mucosa share the pathological and clinical appearances of endometriosis in general.

Most recently "metaplasia of cervical epithelium" into endometrial form, has been invoked by Novak and Hoge⁶ as a cause of the surface type of cervical endometriosis. In Cases 5 and 7 of this series, both endometrial and endocervical cells segmentally comprised the lining surface of large glands. The stromatogenous mantle, however, only appeared beneath those epithelial cells bearing an endometrial configuration (Figs. 1 and 2).

Endocervical endometriosis at or near the internal os is worthy of special comment. Grossly, the lesion comprises small single or multiple cysts with either clear or hemorrhagic fluid occasionally accentuated by a concentric hemorrhagic stromatogenous mantle. Microscopically, the glands comprising the lesion lie beneath the endocervical lining mucosa, mingle with the cervical forms, and even extend into the fibromuscular layer. In many glands the lining cells are narrow and of medium height. The cell cytoplasm is scant and the cell border is poorly defined. The large ovoid, deeply staining nucleus reaches from the basement membrane to the free border. Other glands

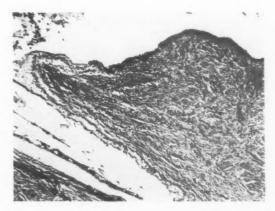


Fig. 2. (Case 7; 1744.) Cervical endometriosis caused by "epithelial mutation." A large cervical gland presents a broad, papillary infold. Its upper surface is clothed by a layer of classical endometrial cells. A narrow mantle of round stromatogenous cells is present. The tip of the fold and its inferior aspect are covered by cells of endocervical type. (×60; reduced approximately 1/3.)

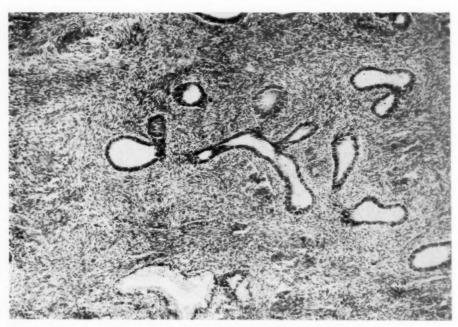


Fig. 3. (Case 2; 54-4129.) Endocervical endometriosis at the internal os due to "developmental fault." Round, oval, and elongated glands are intermingled with classical cervical forms. Sacculation is prominent. Note the secretory, clear, and peg cells indicating tubal prosoplasia. A cytogenous mantle is lacking. Heterotopia and tubal prosoplasia are prominent in this form of endocervical endometriosis. (×100; reduced ½.)

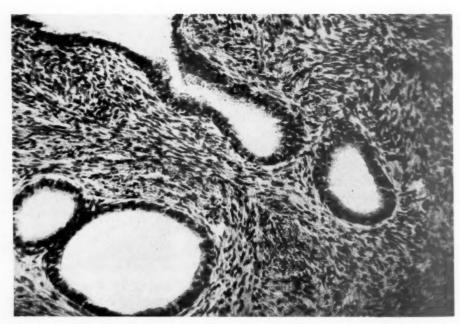


Fig. 4. (Case 2; 54-4129.) Endocervical endometriosis due to "developmental fault." The clear, ciliated, and peg cells indicative of tubal morphological conditions are well shown. There is no distinct cytogenous mantle. The cervical stromal cells however are concentrically arranged about the glands. (×250; reduced 1/4.)

present secretory, peg, and clear cells bearing the stigmas of tubal mucosa (Figs. 3 and 4). Other glands more closely approach endometrial morphology. It is inferred that this form of endocervical endometriosis, etiologically ascribed to "developmental fault," results from heterotopic growth of isthmic uterine glands into the fibromuscular layer of the cervix and downward extension caudad to the histological internal os. The presence of tubal lining cells indicates concomitant prosoplasia. Although this class of endometriosis appears of primary origin, when it was found in association with ovarian or pelvic endometriosis it was arbitrarily grouped under secondary endometriosis.

Analysis of cases

In keeping with the above criteria, this series of 17 cases of cervical endometriosis was comprised of 12 primary and 5 secondary cases. Of the former, 8 involved the ectocervix while 4 presented as endocervical lesions (Tables I and II). Because of antecedent pregnancy and labor, 5 of the 8 ectocervical forms were deemed due to "cervical trauma and endometrial implantation" and one followed curettage for endometrial hyperplasia. Two were considered the result of "developmental ectopia," one presenting as an ulcer in the anterior fornix at the cervicovaginal junction and the second as a deep-lying nodule discovered upon palpation at the junction of the posterior cervix and posterior fornix. Of the 4 primary endocervical cases, 2 had microscopic evidence of origin by "mutation." The third patient presented a lesion at the internal os which was considered the result of "heterotopic fault." In Case 4 absolute classification could not be made. Although the presence of an endometrial surface lining and an associated endometrial polyp just above the external os suggested origin by "ectopia" or "mutation," an antecedent full-term pregnancy and delivery would not preclude origin by "trauma and implantation" (Figs. 5A and 5B). Of 6 secondary endometriomas encountered in 5 patients, 3 were ectocervical and 3 endocervical in location. All

Table I. Classification of primary cervical endometriosis

Etiology	Ecto- cervical	Endo- cervical
Ectopia	2	0
Heterotopic fault at internal os	0	1
Tissue trauma with subsequent endometrial implantation	6	0
Mutation of cervical into endometrial cells	0	2
Unclassified	0	1

Table II. Classification of secondary cervical endometriosis

Etiology	Ecto- cervical	Endo- cervical	
Descent of corporeal stro- matosis or adenomyosis interna	0	0	
Heterotopic fault at internal	0	1#	
Direct extension from peri- toneum or supravaginal cervix or rectovaginal			
septum	0	0	
Hematogenic or lymphogenic spread	3*	2	

*In Case 3 initial removal of the secondary ectocervical bleb was followed by hysterectomy for severe pain due to the primary ovarian endometriosis. An endocervical "heterotopic endometrioma" was present at the internal os and was accordingly grouped as secondary in type.

were attributed to hematogenic or lymphogenic spread from a primary lesion elsewhere in the pelvis. In Case 3 a secondary ectocervical bleb was initially removed. Hysterectomy was later necessitated by severe comenstrual pain resulting from primary bilateral ovarian endometriosis. The "heterotopic fault" lesion discovered at the internal os was classified as secondary in type because of ovarian endometriosis.

Pathology of cervical endometriosis

Irrespective of type, location, or etiology, the gross appearance of cervical endometriosis is similar, for capillary congestion and subsequent hemorrhage resulting from hormonal stimulation are the basic factors. With mild stromal bleeding, ectocervical endo-

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Table III. Analysis of cases

Case No.	Hospital No.	Age	Parity	No. of abortions	Curet-	Location	Clinical appearance
Primar	y cervical en	dometri	iosis				
1	53-772	44	2	None	None	Ectocervix	Cervical tear; endometriosis not seen clinically
4	56-1866	46	3	2	None	Endocervix	Not seen clinically
5	57-3411	49	1	None	None	Hemorrhagic cyst above external os	Not seen clinically
6	56-6064	24	1	None	None	Ectocervix	Hemorrhagic blebs beneath e tocervical mucosa
7	58-1744	41	5	3	None	Endocervix and ecto- cervix	Not seen clinically
8	58-3329	41	3	2	?	Ectocervix	Not seen clinically
9	M 1769	22	3	1	2	Ectocervix	Hemorrhagic cyst, anterior l
12	G 3806	29	3	None	None	Junction fornix and ectocervix	Irregular ulcer with red gra
14	58-6489	35	1 (CS)	None	None	Endocervix	Not seen clinically
15	55-2374	35	1	None	None	Ectocervix	Punctate hemorrhages on poterior ectocervix and on fornix
16	49-2017	44	1	None	None	Ectocervix	Firm, fixed 15 mm. nodule junction cervix and poster fornix
17	59-914	49	None	None	None	Ectocervix	3 mm. red bleb midway be- tween external os and vau
Second	lary cervical	endom	etriosis				
2	54-4129	29	1	1	1	Endocervix in super- ficial fibromuscular layer	Not seen clinically
3	55-5170 56-2269	35	2	None	None	Ectocervix in biopsy; endocervix in hys- terectomy specimen	Purple nodule, 4-5 mm. on right lateral segment

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-	pecimen received	Pathology	Associated pathology	Presumed etiology	
iosis	Uterus, adnexa	Stroma well formed; no hem- orrhage; glands hyper- plastic	Endometrial hyper- plasia and leiomy- omas	Tissue trauma and subsequent endometrial implantation	
۱	Uterus, adnexa	Endometrial polyp in endo- cervical canal; stroma well formed; no hemorrhage; glands nonfunctional	Healing erosion; leio- myomas	Unclassified	
	Uterus, adnexa	Stroma well formed with hemorrhage; glands hyper- plastic and some contain both endocervical and en- dometrial cells	Leiomyomas; endometrial polyp	Mutation of endocervical into endometrial cells	
ath ec-	Curettings, cervix biopsy	Stroma edematous, well formed; recent hemor- rhage; glands in secretory phase	Cystic ovaries	Tissue trauma with subsequent endometrial implantation	
	Uterus, adnexa	Stroma well formed; recent hemorrhage; glands mid- interval; tubal metaplasia	Pyosalpinx	Mutation of endocervical into endometrial cells	
	Uterus, adnexa	Stroma poorly formed with recent hemorrhage; glands nonfunctional	Leiomyomas	Tissue trauma with subsequent endometrial implantation	
erior lip	Curettings, cervix biopsy	Stroma of predecidual type with mild hemorrhage; glands in late secretory phase	None	Tissue trauma with subsequent endometrial implantation	
ed gran-	Biopsy	Stroma scant; no hemor- rhage; glands with cystic hyperplasia	None	Ectopia	
	Uterus, adnexa	Stroma scant; no hemor- rhage; glands hyperplastic	Leiomyomas; cervicitis	Heterotopic fault	
on pos- d on	Curettings, cervix biopsy	Stroma well formed with old and recent hemorrhage; glands hyperplastic	Simple endometrial hy- perplasia and polyp	Tissue trauma with subsequent endometrial implantation	
odule posterio	Amputated cervix	Stroma scant; no hemor- rhage; glands with cystic hyperplasia	Hysterectomy 8 years before for leiomy- omas; tubes and ovaries retained	Primary ectocervical and vaginal ectopia	
y be- nel vault	Biopsy	Stroma moderate; no hemor- rhage; glands hyperplastic	Endometrial hyper- plasia 1 year before	Tissue trauma with subsequent endometrial implantation	
	Uterns, adnexa	Stroma well formed and edematous; no hemor- rhage; tubal metaplasia present	Leiomyomas; endo- metriosis cul-de-sac, ovaries, tubes, pelvis	Hematogenous spread to cervix	
t	Curettings, cervix bi- opsy; uterus, adnexa 6 months later	Secretory glands; well- formed stroma with recent hemorrhage in biopsy; area of endometriosis noted near internal os in excised uterus	Endometrial polyp; bi- lateral ovarian endo- metriosis	Hematogenous spread to cervix	

Table III-Cont'd

Case No.	Hospital No.	Age	Parity	No. of abortions	Curet- tage	Location	Clinical appearance
10	M 4282 55-3099 55-6298	35	1	None	None	Ectocervix	Punctate hemorrhages
11	54-5716	45	1	1	None	Ectocervix	Several purple, 3-4 mm. nod- ules on anterior lip
13	56-380 58-6011	47	3	None	None	Endocervix	Hemorrhagic cysts with brown, syrupy material seen in ex- cised uterus

metriosis appears as minute, solitary, or multiple ecchymotic foci and/or papules which involve one or both cervical lips. The bright red color in the premenstrual phase and the purple tint after completion of the menses are noteworthy. Stromal hemorrhage which is more abundant and/or circumscribed, causes elevation of the overlying epithelium with the formation of a hemorrhagic bleb (Fig. 6). Subsequent necrosis and detachment of the surface epithelium produces an irregular ulcer with an uneven, granular base. On rare occasions, continued growth of the component glands and stroma in the ulcer bed produces papillary lesions



Fig. 5A. (Case 4; 56-1866.) The squamous lining of the ectocervix terminates abruptly and is continuous with a solitary layer of endometrial lining cells which proceed into the cervical canal. The small, deeply staining lobate structure represents the polyp noted in Fig. 5B. (×10; reduced 3/5.)

which simulate carcinoma. Spontaneous healing of the ulcer is associated with excessive fibrosis and a thickened and puckered scar. When bleeding into gland spaces is dominant and the latter are numerous or closely set, the resultant distention of their lumina produces a mulberry-like lesion, the restricted expansion of the supporting stroma causing the crenations between the bulging glands. More deeply lying endometriotic lesions appear as firm or cystic nodules (Fig. 7). Tinctorial changes resulting from bleeding are obscured because of their deeper location. Of two endocervical endometriomas arising by "epithelial mutation" that of Case 5 presented as a hemorrhagic cyst, 4 mm. in diameter, lying in the endocervical mucosa just above the internal os. That in Case 7 was a chance microscopic discovery. The endometrial polyp of the cervix in Case 4 was not seen grossly. The "heterotopic fault" endometriomas of the internal os presenting as clear or hemorrhagic cysts occasionally encompassed by crescentic mantles of hemorrhagic stroma were revealed by gross section of the extirpated cervix.

The microscopic characters of cervical endometriosis are well known. They comprise varying proportions of endometrial glands stroma, and capillaries, the stroma generally predominating. The glands according to their morphology are designated as nonfunctional, functional, or hyperplastic. When avaliable, the microscopic appearance of the uterine mucosa in the individual case expe-

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St. cimen received	Pathology	Associated pathology	Presumed etiology
Cervix biopsy; supra- cervical hysterectomy 2½ years later	Stroma decidua-like; no hem- orrhage; glands in premen- strual phase	Leiomyomas; endo- metriosis right ovary and peritoneum	Hematogenous spread to cervix
Curettings, cervix biopsy	Stroma poorly formed; no hemorrhage; endometrial glands hyperplastic	Endometriosis left ovary suspected clin- ically	Hematogenous spread to cervix
Curettings, cervix bi- opsy; uterus, adnexa 3 years later	Stroma scant with old hemor- rhage; glands in late secretory phase	Leiomyomas; external uterine adenomyosis; no lesion in ovaries or peritoneum	Hematogenous spread to cervix

dites such classification. The morphology of nonfunctional endometrial glands and stroma requires little discussion. Functioning glands are readily identifiable, especially in the premenstrual stage, by their serration, eosinophilic nature of the lining cells, and accumulated secretion in the gland spaces. Hyperplastic glands either grouped or widely separated often display variation in size and

contour. Smaller round or oval glands are frequently intermingled. In all hyperplastic glands, however, the lining cells are enlarged and contain an increased amount of cytoplasm surrounding a large, deeply staining nucleus. In this series 2 cases presented glands of the nonfunctional type; 8 displayed the morphology of hyperplasia, and 4 the features of the secretory phase (Figs. 8

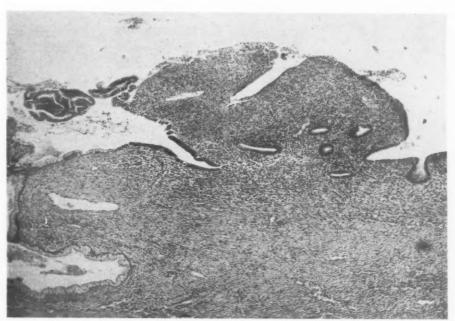


Fig. 5B. To the right the lining of the endocervix is formed by ectopic endometrium. The central polyp presents a wide base. Its stromal matrix contains classical endometrial glands. The capillaries are prominent. To the left the endometrial lining cells are continuous with endocervical cells. Although mutation or ectopia are likely factors, antecedent pregnancy allows origin by "trauma and implantation." This case remains etiologically unclassified. (×100; reduced 1/4.)

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Fig. 6. (Case 6; 56-6064.) Microscopic appearance of a hemorrhagic bleb in ectocervical endometriosis. Hemorrhage obscures the stromatogenous mantle. The overlying spuamous epithelium is detached, elevated, and focally ruptured. Glands and stroma were present in adjoining fields (see Fig. 9). (×100; reduced 3/5.)

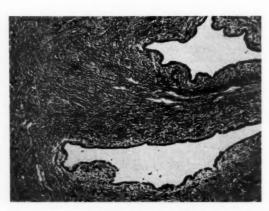


Fig. 7. (Case 16; 59-2067.) Primary "ectopia" in ectocervical endometrioma. The nodular lesion was palpated at the junction of the posterior cervix and the vaginal vault. Its glands are irregular and wavy and lie in a fibromuscular wall. The lining endometrial cells are classical. The stromatogenous mantle is well-developed. (×60; reduced approximately 1/3.)

and 9). Case 3 revealed glands of tubal character as evidenced by the presence of secretory, peg, and clear cells in the lining epithelium (Fig. 10). Cases 5 and 7 prosented cervical glands of "mutation form" as evidenced by the coincidental presence of endocervical and endometrial lining cells (Figs. 1 and 2). Hemorrhage into the gland spaces was noted in 5 cases and was generally scant. The stromatogenous mantle was only roughly estimated and was considered well formed in 11 cases and scant or poorly formed in the remaining 6. Endocervical endometriomas in the region of the internal os generally displayed poor stromal formation. Functional changes were evidenced by the presence of large, round, and even predecidual cells, in the latter instance in association with classically serrated glands of the premenstrual phase (Fig. 11). Stromal hemorrhage was lacking in 8 cases. Seven patients presented evidence of recent bleeding and 2 displayed hemolyzed red blood cells, one in association with large numbers siderophages. Capillaries frequently reached sinusoidal dimension in functional endometriomas showing premenstrual changes. Often they were obscured by stromal hemorrhage resulting from their rupture.

Clinical features

The symptoms of cervical endometriosis are difficult to evaluate because of their frequent association with other lesions of the uterus. Thus, fibromyomas occurred in 8 patients, and fibromyomas with associated endometrial hyperplasia in 2 others. Endometrial polyps were encountered in 5 additional instances. The age distribution of the lesion is of interest. Three occurred tween the ages of 20 and 30, 4 between 30 and 40, and 10 between the ages of and 50. In view of the gross and microscopic pathology, premenstrual staining or spottil was the anticipated complaint and coild trauma and bleeding a decided possibility in exposed ectocervical lesions. Endometra omas confined to the endocervix or thoplaced high upon the ectocervix or in the

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vaginal fornices were beyond reach of coital tauma. The complaint of premenstrual staining alone was encountered 4 times among 11 patients with exposed sizable ectocervical lesions, and one other reported both pre- and postmenstrual staining and also the presence of postcoital bleeding (Table III). The remaining 6 patients were symptom-free. Of 6 patients with endocervical lesions, bleeding was encountered in only 2 (Table III). One of the patients presented a concomitant endometrial polyp, evidently the source of the bleeding; while in Case 4 the endometrial polyp was ectopically placed in the endocervix just above the external os. In endometriosis of secondary origin the complaints of menstrual backache, comenstrual abdominal pain, dyschesia, dyspareunia, etc., were evidently the manifestations of the primary lesion located elsewhere in the pelvis.

The clinical diagnosis of cervical endometriosis is not easy unless exposed position and a lesion of sufficient size is present. Thus, in only 9 patients was endometriosis clinically recognized or suspected. Of these, in 5 the endometriosis presented as ecchymotic lesions and/or hemorrhagic papules, and in 2 as hemorrhagic blebs. A superficial ulcer placed anteriorly at the cervicovaginal junction was proved by biopsy. Palpation disclosed the deep endometriotic lesion of the posterior ectocervix at its junction with the vaginal wall. Of the 8 cases clinically undetected, 3 were endocervical and were first revealed by gross section of the extirpated cervix. The remaining 5 were microscopic findings in the laboratory. Greater frequency in clinical detection of ecrocervical endometriosis could be achieved by examination made in the late premenstrual phase as suggested by Williams and Richardson.⁹ The use of punch biopsy for all hemorrhagic lesions as suggested by Ranney and Chung⁷ affords another clinical

Definitive treatment of cervical endometriosis could be applied only to lesions which were clinically recognized or suspected. In 5 of 9 ectocervical cases where biopsy was initially performed for diagnosis, the disease was completely eradicated by this procedure alone. In another patient subsequent cauterization was necessary for destruction of residual disease. One (Case 17) is too recent for evaluation. Crescentic segmental excision was employed in one case for multiple endometriotic lesions involving the anterior and posterior cervical lips. The deeplying nodule presenting in the posterior cervicovaginal junction as also the superficial ulcer in the anterior fornix were removed by simple excision. Two of the secondary ectocervical lesions required subsequent hysterectomy because of severe abdominal pain resulting from endometriosis of the ovaries. No residue of the cervical endometrioma was found in Case 3. In Case 10 only supracervical hysterectomy could be performed, but the retained cervix was clinically free from disease.

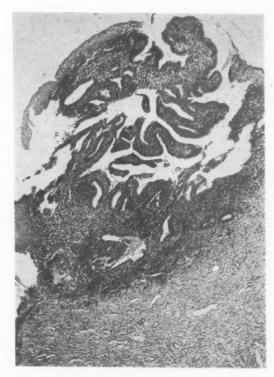


Fig. 8. (Case 17; 59-914.) Ectocervical endometriosis originating by "trauma and implantation," after curettage for glandular cystic hyperplasia. The overlying squamous lining is partially preserved. The underlying mantle of endometrial stromal cells encases large and irregular hyperplastic endometrial glands. (×100; reduced 3/5.)

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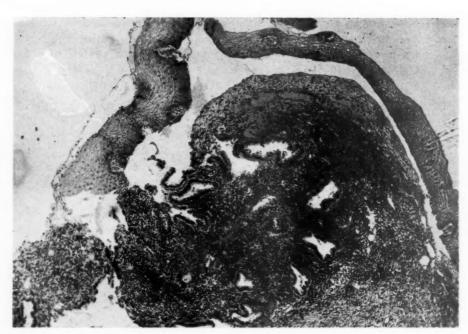


Fig. 9. (Case 6; 56-5064.) Function in primary ectocervical endometriosis. Section was taken adjacent to the hemorrhagic bleb depicted in Fig. 6. The glands are tortuous and lined by tall cells with subnuclear vacuolization. The nuclei are somewhat displaced toward the free cell border. The round cell stroma contains large numbers of preserved red blood cells. (×100; reduced 1/4.)

Summary and conclusions

1. Cervical endometriosis consists of primary and secondary types; the former originate in the cervix, the latter reach this site by lymphatic and/or hematogenic spread from the primary lesions elsewhere in the pelvis. Both present ectocervical and endocervical forms. Primary ectocervical endometrioma is most common.

2. Primary cervical endometriosis arises as follows: (1) by surface trauma (incurred during delivery or after operation), followed by subsequent implantation and growth of detached endometrial fragments; (2) by "developmental ectopia"—cell rests from the Müllerian tubercle of the primary vaginal plate remain on or beneath the lining epithelium of the upper vagina, its fornices, or infravaginal cervix, with later formation of endometriomas; (3) by metaplasia of endocervical into endometrial cells with sequential development of a stromatogenous mantle; (4) by "developmental heterotopic fault"—glands of the isthmus uteri are dis-

placed into the fibromuscular wall of the cervix and extend caudad to the histological internal os. Tubal prosoplasia of the glands

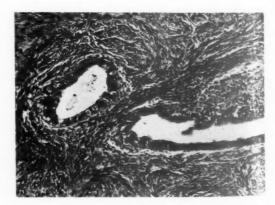


Fig. 10. (Case 3; 56-2269.) Tubal prosoplasia in endocervical endometriosis. The ectocervical hemorrhagic nodule initially present was removed by biopsy (55-5170). Subsequent hysterectomy was necessitated by severe comenstrual pain resulting from primary ovarian endometriosis. This "heterotopic fault" lesion encountered at the internal os was therefore classified as secondary endometriosis. (×100; reduced approximately ½).

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3. Cervical endometriosis of the secondary type arises (1) by descent of uterine stromatosis or adenomyosis interna into the cervix; (2) by lymphatic and hematogenic spread from primary lesions elsewhere in the pelvis; (3) by direct extension from lesions in the cul-de-sac or rectovaginal septum.

4. Cervical endometriosis is frequently associated with uterine fibromyomas and endometrial polyps.

5. The microscopic features of cervical endometriosis are not unusual. The component glands may be nonfunctional, functional, or hyperplastic. Glands with tubal morphological conditions are frequent. The stromatogenous mantle is of varying thickness.

6. A low ectocervical site and a sizable functioning lesion are the necessary requisites for symptoms and diagnosis. Pre- and postmenstrual staining associated with postcoital bleeding are the usual complaints.

7. Clinically, endometriosis of the ectocervix appears as minute, ecchymotic foci, hemorrhagic papules and/or blebs, and less commonly as superficial ulcers or subepithelial cysts or nodules. Endocervical lesions escape clinical recognition.

8. Cauterization or segmental excision of ectocervical lesions of primary or secondary forms yield excellent therapeutic results.

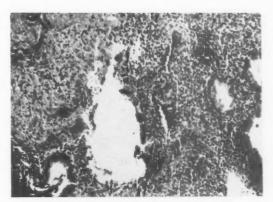


Fig. 11. (Case 10; M 4282.) Decidual changes in the stroma of an ectocervical endometrioma. The stromal cells are round, oval, or fusiform and present a sharply defined cell membrane. The nucleus is central and vesicular in type. The pallor of the cytoplasm and its finely granular character are noteworthy. (×100; reduced approximately $\frac{1}{3}$.)

9. Secondary cervical endometriosis may require complete hysterectomy and bilateral salpingo-oophorectomy if abdominal pain, etc., due to the primary pelvic lesion is dominant.

Thanks are extended to Drs. I. Neigus, S. Kraushar, C. Birnberg, J. T. Davis, B. I. Gilson, T. H. Grundfast, M. Shir, and P. Pedowitz for permission to include their cases, and to Mr. Marvin Ehlin, Miss Esther Torres, and Mr. J. Illari for the photomicrographs.

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Benign tumors of the uterine cervix

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IN RECENT years there have been a number of articles on benign tumors of the uterine cervix; however, these studies have dealt with only one or two types of cervical tumors or have been single or multiple case reports. The incidence of benign tumors of the cervix in a given series of cases has been reported just once to our knowledge. In 1932 Davis¹ presented the statistics on biopsy material from 1,200 cervices. He found 34 benign neoplasms including 26 polyps, 7 myomas, and one fibroma. It is interesting to note that there were no cases of endometriosis, papilloma, or granuloma. Because of the paucity of articles on these tumors as a group, we thought it would be of some interest to describe our observations on the types and relative frequency of benign cervical neoplasms.

Benign tumors may arise from any of the normal cervical components including the ectocervical and endocervical epitheliums, fibrous and muscular elements, vascular structures, and mesonephric remnants. Also, small tumors may result from regions of benign endometrial implantation. Often cervical tumors are incidental to other pelvic lesions requiring operation, and they frequently may be very small and asymptomatic. For these reasons their incidence in any given series will not only depend on the size and number of tumors, but also upon

the frequency with which cervical biopsy is employed, the accuracy with which the blocks from cervical specimens are selected and cut, and the number of sections examined.

Material

All of the material reported is from the files of the laboratory of the Department of Obstetrics and Gynecology of Northwestern Medical School from 1938 to 1958. The total number of obstetrical and gynecological specimens examined during this interval has been 24,666. Since a number of these specimens did not include a portion of cervix for histologic study, we are unable to give a figure for the number of individual cervical specimens examined during this 20 year period.

Some cases have been reported previously in other articles from this department on specific tumors of the cervix. They include endometriosis,² squamous papillomas,³ hemangiomas,⁴ and mesonephric structures.⁵ The material from these articles has been added where indicated for statistical purposes.

With the exception of cervical polyps, the gross and microscopic reports and histologic specimens were reviewed in all cases in which they were avaliable. Additional blocks and differential stains were occasionally necessary, particularly in some cases of endometriosis. A few cases were omitted when the original diagnosis was in doubt or could not be confirmed.

We eliminated Nabothian cysts from the discussion, although they are surely the most common tumefaction of the cervix.

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because of the high frequency of this concition and its likely precursor, chronic cervicitis or endocervicitis, these diagnoses are not included in our statistical files and we are unable to give a figure for the frequency of these cysts. However, Davis¹ reported a 31 per cent incidence in biopsy material alone, and if the entire cervix were available for histologic study the incidence would be considerably higher.

Table I lists the number of tumors of each type found in the study.

In addition to true tumors we have included a discussion of two proliferative conditions of the cervix which simulate tumors to some extent. These proliferative lesions are adenosis or adenomatoid hyperplasia of endocervical glands and mesonephric remnants.

Finally, we will discuss a few unusual cervical tumors which we have not seen but which have been documented in the literature.

Cervical polyps. There were 1,056 cervical polyps for an incidence of 4.3 per cent. This incidence may be compared with that reported for comparable series, namely, 1.5 per cent,6 2.4 per cent,7 5 per cent,8 and 10 per cent.9 Because of the type of samples evaluated, these figures are higher than the incidence of cervical polyps in the general population.

All but three of the 1,056 polyps arose in the endocervix and were characterized by a loose fibrous stroma usually containing varying numbers of endocervical glands. The surface epithelium was of the endocervical type. Some degree of infection and necrosis was common in these polyps, and the incidence has been variously reported at from 65 per cent¹⁰ to 79 per cent.¹¹ The three polyps which originated on the portio vaginalis had a more solid fibrous stroma and were covered by normal squamous epithelium.

Ten of the polyps revealed significant decidual changes in association with pregnancy. There was also one true decidual polyp which consisted of a stroma of decidual cells covered by endocervical epithelium.



Fig. 1. Cervical polyp with extensive squamous metaplasia involving both surface and glandular epithelium. (×15; reduced approximately ½.)



Fig. 2. Higher power magnification of Fig. 1. Note the numerous glandlike spaces in the various plaques of squamous epithelium. (×90; reduced approximately ½).)

Table I

Cervical polyps	1,056	(4.30%)
Squamous papillomas	58	(0.24%)
Endometriosis	44	(0.18%)
Myomas	42	(0.17%)
Granulomas	4	(<0.02%)
Adenomyomas	2	(<0.01%)
Fibroadenomas	2	(<0.01%)
Hemangiomas	2	(<0.01%)
Squamous inclusion cysts	2	(<0.01%)
Total benign tumors	1,212	(4.91%)
Total gynecological and ob-	stetrical	24,666

A few cases of decidual change in cervical polyps have been described.¹² In addition, polypoid decidua has been reported,¹³ and such lesions may resemble carcinoma.¹⁴

Squamous metaplasia was found in 128 or 12.2 per cent of our cases. This compares with an incidence in other series of 8.5 per cent,7 29 per cent,15 and 31 per cent.16 While squamous metaplasia involving the surface or glandular epithelium of a cervical polyp is not an uncommon finding, it is important, although seldom difficult, to differentiate these epithelial changes from carcinoma arising in a polyp (Figs. 1 and 2). Even in the presence of marked or atypical metaplasia, polyps may be treated conservatively. TeLinde¹⁷ reported that of 24 suspicious microscopic cervical lesions, 12 occurred in polyps. These lesions were removed by local excision and the patients were followed one to 10 years without evidence of recurrence.

Malignant change in a cervical polyp is extremely rare. We have had two carcinomas which apparently arose in a polyp; an incidence of 0.2 per cent. One was an adenocarcinoma and the other was squamous in type. This incidence compares closely with the 0.2 to 0.4 per cent incidence reported by other authors. 16, 18-20

Squamous papillomas. There were 58 instances of squamous papillomas in the present series, of which 26 were reported in detail in 1954.³ This series and those of other investigators²¹⁻²⁴ indicate that these tumors of the cervix are more common than once suggested.^{25, 26} The addition of the

present group of cases makes a total of 205 cases of cervical papilloma in the literature to date.

The etiology of papillomas is far from clarified, although numerous factors have been cited. Gonorrhea and genital tuberculosis were believed to be common precursors,26,27 but in our material these specific inflammatory causes have not been evident. The presumed relationship of viruses to certain papillomas including the verrucous type and condyloma acuminata has been reported.18, 23, 28 Chronic and nonspecific inflammation secondary to gonorrhea or mechanical irritation has been considered an etiological agent.29 It has also been claimed that an increase in anterior pituitary hormone may cause epithelial proliferation and predisposition to papillomas. 80 Hyperplasia and papillary lesions of the cervical epithelium during pregnancy have been reported by Edmondson and associates, 31 Galloway,32 and Johnson.33 However, Carrow and Greene³⁴ found no papillary outgrowths or epithelial changes specifically related to pregnancy, although they did note an occasional increase in thickness of the squamous epithelium, particularly in the basal layers.

Papillomas of the cervix have been classified in many ways varying from etiological aspects to gross and microscopic characteristics. We have used the same histologic criteria for the diagnosis and classification of cervical papillomas as Greene and Peckham,3 and we refer the reader to their article for details. The most frequent histologic changes occur in the basal layers of the thickened squamous epithelium where there is found an increase in cellularity and mitotic activity (Figs. 3 and 4). The more superficial epithelium also may be involved. and the degree in which these changes occur determines the diagnosis of typical or atypical papilloma. With this method cervical papillomas have been divided into three categories: (1) typical papillomas; (2) atypical papillomas; and (3) papillomas coexisting with epithelial abnormalities in other areas of the cervix. A number of)5

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attempts have been made to classify and differentiate condyloma acuminata and squamous papillomas of the cervix. Goforth²¹ and Woodruff and Peterson³⁵ have presented the microscopic features considered important in differentiating condyloma acuminata from papillomas of the cervix, but most authors feel that the two lesions are histologically indistinguishable. In unpublished data from this department we were unable to differentiate accurately cervical papillomas from condyloma acuminata by means of the microscopic criteria outlined by Woodruff and Peterson and are inclined to feel justified in including both lesions in one category of squamous papillomas. Marsh24 perhaps has the most reliable criterion in that the only papillary lesions of the cervix which are classified as condyloma acuminata are those that are associated with other genital condyloma acuminata.

There were 38 cases of so-called typical papillomas including 4 cases associated with



Fig. 3. Typical squamous papilloma of the cervix with papillomatosis and acanthosis. (×35; reduced approximately 1/3.)

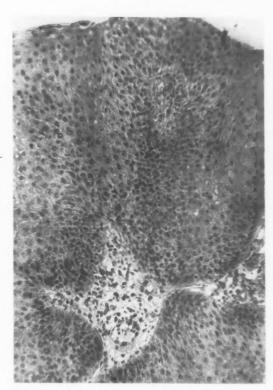


Fig. 4. Higher power magnification of Fig. 3. Mitoses are limited to the basal layers of the squamous epithelium. (×100; reduced approximately 2/5.)

condyloma acuminata of the vagina or vulva. These lesions were usually small single papillary elevations which revealed branching and vascular papillae covered by squamous epithelium with varying degrees of acanthosis, parakeratosis, hyperkeratosis, and infiltration by leukocytes. The basal layer of epithelium was slightly thickened. Mitotic figures and double and triple nuclear forms were more frequent than in normal epithelium, but were limited to the basal layers. No abnormalities were noted in the cervical epithelium adjacent to the papillomas.

There were 11 atypical papillomas which contained definite epithelial abnormalities. Seven showed evidence of basal cell hyperplasia, and 3 contained lesions involving the full thickness of the epithelium, but with insufficient cellular change to be classified as preinvasive cancer. They were called "equivocal lesions." The eleventh and previously reported case was markedly atypical but was considered to be benign. This was a diagnostic error, and subsequently the patient was found to have invasive squamous cell carcinoma of the cervix which caused her death.

Nine typical papillomas coexisted with other tissue changes in the adjacent epithelium. Basal cell hyperplasia was present in 3 cases and preinvasive carcinoma in 3 other cases. The remaining 3 papillomas were adjacent to equivocal lesions.

Although 72.4 per cent of the patients with papillomas were pregnant as compared to approximately 50 per cent in other series,^{21, 24} there is no apparent causal relationship between pregnancy and papillomas of the cervix. We attribute our higher figure to the fact that we have performed a large number of biopsies of the cervix in obstetric patients. Also, papillomas in pregnancy tend to be somewhat larger,^{3, 31} and this in turn may increase the incidence of biopsy and diagnosis of these lesions during pregnancy.

If not completely removed at the time of biopsy the remaining portion of most papillomas seems to regress. There were 24 cases with a satisfactory follow-up and in all instances the papilloma eventually disappeared on gross or histologic examination.

In 1922 Meyer²⁵ stated that the usually recognized forms of papilloma are apparently enduringly benign. We also feel that papillomas are not premalignant, but that it is important to differentiate them from cervical squamous carcinoma. A case previously described in this section, in which an invasive carcinoma was erroneously diagnosed as an atypical papilloma, bears this out. Other cases have also been described where papillomas were at least temporarily mistaken for carcinoma.31, 36 Kazal and Long,22 in reviewing the literature and their material, found 7 cases in a total of 134 in which a papilloma was considered to have undergone transformation to carcinoma. These 7 cases occurred in solitary papillomas and none were related to preg-



Fig. 5. Endometriosis of the cervix. Endometrial glands and stroma are evident beneath the cervical squamous epithelium. (×28; reduced approximately ¼.)

nancy. In our 58 cases only one papilloma may have undergone change to carcinoma, although in retrospect it may have been carcinoma from its inception. Thus, 8, or 3.9 per cent, of 205 papillomas were thought possibly to have transformed to carcinoma; and, while atypical changes in or adjacent to papillomas are not unusual, these cervical tumors must be considered predominantly benign.

Follow-up of the associated and coexisting abnormal lesions in the series is of interest. There were 6 equivocal lesions. Three arose in atypical papillomas, and the 2 patients who were not pregnant were unfortunately lost to follow-up. The third case was in a pregnant patient and the lesion had disappeared by the time of the postpartum examination. The other 3 equivocal lesions were in the adjacent epithelium. In the 2 patients who were not pregnant, the equivocal lesion or the papilloma could not be found on subsequent histologic examination, although there was evidence of basal cell hyperplasia. The third case which was associated with pregnancy later proved to be preinvasive carcinoma and was treated by total hysterectomy. Microscopic examination of the cervix confirmed the preinvala

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sive lesion, but failed to reveal a papilloma.

Three preinvasive carcinomas were found by biopsy to coexist in the epithelium adjacent to typical papillomas, and in each case the patient was pregnant. One case was lost to follow-up and 2 cases were later treated by hysterectomy. Examination of the latter 2 cervices confirmed the preinvasive lesion in one instance and there was a minimally invasive lesion in the other, but in neither case was a papilloma found.

Endometriosis. There have been 44 cases of endometriosis of the cervix in our material, including the 16 cases reported in an earlier publication.² Thirty-seven of these cases were located on the pars vaginalis, and the remaining 7 lesions were in the endocervix and close to the cervical canal. In 30 cases the diagnosis was made by cervical biopsy, and the other 14 cases were diagnosed following histologic examination of hysterectomy specimens. Prior to 1952



Fig. 6. Higher power magnification of Fig. 5. Proliferative glands are seen in a vascular, slightly edematous stroma. (×100; reduced approximately %5.)

there had been only 12 cases reported,² but since then at least two series of cases have been recorded.^{2, 37}

The lesion is believed to be due to the implantation of endometrial tissue fragments into a disrupted area of cervical epithelium. The relative rarity of cervical involvement in the light of the proximity and frequent exposure of the cervix to endometrium at the time of menstruation is explained in part by the absence of optimal conditions for the implantation of endometrium. Hobbs and Lazar38 and Lash and Rappaport³⁹ have outlined these conditions and they include the resistance of intact squamous epithelium to implantation, frequent presence of some degree of cervical inflammation, decrease in pH, and absence of sterile conditions. Hobbs and Bortnick⁴⁰ have noted that humoral factors are probably not of as much importance because other areas commonly involved by endometriosis are exposed to the same humoral concentrations as the cervix.

The lesions have a variable gross appearance. They are usually small and consist of a slightly elevated, blood-filled cyst, or a red, velvety, circumscribed or streaklike lesion. Occasionally, they appear as an erosion or ulcer or deeper cysts which may or may not be visible on inspection. The microscopic description is that of endometrial glands with either columnar or cuboidal epithelium and elongated nuclei (Figs. 5 and 6). The glands may be in a proliferative or secretory phase. Endometrial stromal cells are present although at times they are difficult to identify. Special staining, such as periodic acid-Schiff technique with alpha amylase digestion, is occasionally necessary to distinguish endometrial and endocervical glands, since the mucin-laden cells of endocervical glands will stain deep red with this technique.

Clinically, cervical endometriosis must be differentiated from Nabothian cysts, cervicitis with focal hemorrhage, decidual hemorrhage, hemangiomas, and carcinoma. One case of cervical endometriosis reported in the literature had tentatively been classified as Stage II carcinoma of the cervix before the true diagnosis was established.⁴¹

In addition, certain criteria must be followed to substantiate the diagnosis. They are: (1) the location of the lesion in the endocervix or on the portio beneath the squamous epithelium or exposed on its surface, and (2) the absence of evidence of extension directly into the cervix from the corpus or the rectovaginal septum. For these reasons the definitive diagnosis should be microscopic, and the frequency with which the lesion is found will be directly related to one's awareness of its presence and the number of times cervical biopsies are performed.

Myomas. In reviewing all instances of patients with uterine myomas in our files, we



Fig. 7. Endocervical adenosis. Marked proliferation of endocervical glands with associated chronic cervicitis. (×5; reduced approximately ½3.)

found 42 cases with cervical and 3,310 with fundal myomas. The incidence of patients with these cervical tumors compared to those with myomas of the fundus was 1.2 per cent. The incidence in the literature was found to vary from 0.4 to 15.5 per cent. 42-47 Two of our 42 cases arose in the cervical stump. A myoma arising in a cervical stump is a rare occurrence and was first reported by Giles in 1923. Since that time reports in the literature have revealed an additional 19 cases. 47, 49, 50-58

Cervical myomas arise from the sparse and irregularly distributed muscular tissue of the cervix, and are almost always single and vary from microscopic size to a tumor filling the pelvis. In all of our cases the myomas were single, and in 17 instances they were minute in size. The largest tumor weighed 800 grams. Five of the myomas were polypoid or pedunculated and the remainder were in the cervical stroma or replaced it. Histologic examination of these tumors revealed a varying amount of fibrous and muscular elements. The smaller myomas tended to be more cellular, whereas the degenerative changes were confined to the larger tumors. None of our cases showed sarcomatous change, but this has been reported.49

Although there were no pregnant patients in our group of cases, this association has been well established in the literature.⁵⁴

Treatment of myomas of the cervix is usually hysterectomy because of the high incidence of associated fundal myomas. However, in cases of pedunculated or small intracervical tumors, myomectomy or cervical amputation may be carried out. In this series 33 patients were treated by hysterectomy, 4 by vaginal myomectomy, and 3 by cervical amputation. Two tumors were removed by excision of the cervical stump; once vaginally and once by laparotomy.

Granulomas. In this series there were a granulomas which appeared as proliferative tumefactions on the portio vaginals of the cervix. In our cases there was no evident cause for the granuloma in two instances. A third patient was pregnant but

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without other etiology for the granuloma. The fourth case followed radium application to the cervix for carcinoma and may have been due to trauma associated with that procedure. The cause of granulomatous lesions is usually nonspecific inflammation including trauma or chronic irritation, but also may be specific infection. In regard to the latter, the following infections have been considered in the etiology of cervical granulomas: gonorrhea, ²⁶ syphilis and chancroid, ⁵⁵ tuberculosis, ^{26, 55, 56} and granuloma venereum. ^{55, 57-60} Granuloma pyogenicum of the cervix has also been described. ⁶¹

The lesions may vary from several millimeters in diameter to an exuberant, granular, red papillary growth covering the entire cervix. Histologically, the lesions show numerous capillaries, fibroblasts, and many lymphocytes, monocytes, and plasma cells.

The similarity of some granulomas to carcinoma of the cervix has been described. 62, 63 This should make biopsy mandatory, since the microscopic findings cause no difficulty in distinguishing the two entities.

Adenomyomas and fibroadenomas. We have had 4 such cases. Two of the tumors were fibroadenomas and 2 were adenomyomas. In each instance the tumor contained both connective tissue and muscle elements, and the predominance of one or the other was obvious when differential stains were used. These cervical tumors are uncommon as is evidenced by the fact that we could find only one case report in the recent literature.⁶⁴

Three of the tumors were polypoid and varied from 2 to 6 cm. in diameter. The fourth was a 2 cm. discrete fibroadenoma immediately adjacent to the endocervical canal and was an incidental finding in a hysterectomy specimen. One of the adenomyomas was removed from a patient who was 16 weeks pregnant. It arose in the endocervix and was 6 cm. in diameter. Histologically, it was predominantly myomatous with an adenomatous endocervical gland pattern and a moderate decidual reaction. The patient incidentally carried uneventfully to term.

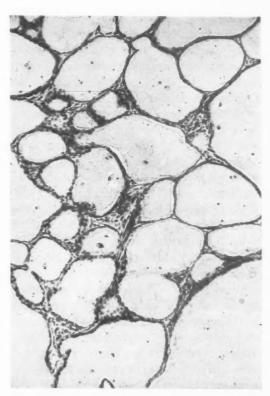


Fig. 8. Higher power magnification of Fig. 7. The cylindrical epithelium has become flattened and the glands have assumed an almost back-to-back arrangement. (×100; reduced approximately ½5.)

These tumors differ from cervical polyps because they are usually larger and have a more firm consistency. The stroma is compact and fibromuscular compared to the loose fibrous stroma of a polyp. Trichrome and mucicarmine stains are often helpful in demonstrating the fibromuscular components and the mucin secreting activity of the glands. Because these tumors may attain a large size they must be differentiated from both pedunculated fundal myomas and the rare polypoid sarcomas of cervical origin. For this reason, as with any polypoid tumor, it is important that they be removed and examined histologically.

Angiomas. We have seen but 2 hemangiomas of the cervix, one of which was previously described in a paper on vascular tumors of the female genital tract.⁴ The other case was a cavernous type of hemangioma found incidentally in a hysterectomy

specimen. It was microscopic and lay deep in the cervical stroma just distal to the internal os. It contained multiple endothelium-lined spaces in which numerous erythrocytes were evident. These spaces were separated by thin fibromuscular septa. Since 1939 there have been a number of cases reported in the literature. 65-69 In 1955 Pedowitz, Felmus, and Grayzel, 70 in an extensive review of the literature, found 138 cases of vasular tumors of the uterus including 17 hemangiomas of the cervix.

Hemangiomas may be of a capillary or cavernous type and range from microscopic in size to a tumor covering the entire cervix. They are often raised, discrete, soft, and violaceous with areas that blanch when pressure is applied. The tumors consist of capillaries or larger endothelium-lined spaces separated by thin connective tissue septa. Blood cells may be evident in the lumina of the vessels. These vascular tumors are usually asymptomatic unless located on the pars vaginalis in which case intermenstrual or postcoital bleeding may be a complaint. The diagnosis is often suggested on gross examination of the cervix which includes a test of blanching; however, histologic findings are the most important findings.

Since many of these tumors may be incidental findings in operative specimens, treatment is not a problem. Operation is indicated by the symptoms or the size of the tumor that is present.

Hemolymphangioma has been reported once,⁷¹ and lymphangioma of the cervix has not been reported to our knowledge, although Plaut⁷² described a 3 cm. polypoid tumor of the endocervix which he classified as a lymphangiocystic fibroma. None of the above entities has been noted in our material.

Squamous inclusion cysts. We have had 2 such cysts in our material and were able to find just one reference in the literature to these squamous cysts.⁷³ Surely this is not a true picture of their incidence.

The cause of these cysts is usually previous operations on the cervix, or trauma



Fig. 9. Mesonephric adenosis. Tubule and ductlike structures located in the mid and lateral portions of the cervix. (×130; reduced approximately 3/5.)

and laceration of the cervix at the time of delivery. Rarely, they may be caused by congenitally misplaced portions of squamous epithelium.

Both cysts occurred beneath the portio of the cervix and were 1 to 2 cm. in diameter and unilocular. They were lined by typical squamous epithelium. The possibility of squamous metaplasia involving a dilated endocervical gland was considered but seemed unlikely in view of the uniformity and similarity of the epithelium to a normal squamous pattern. One case involved a 38-year-old multipara without previous pelvic operation. The cyst was excised locally, and its etiology was very likely obstetric trauma with cervical laceration. The other case was in a 42-year-old nulligravida without previous operative procedure. The cyst was an incidental finding in a hysterectomy specimen and a congenital origin of the cyst was considered most likely.

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Endocervical and mesonephric adenosis. Adenosis or adenomatoid hyperplasia of endocervical glands and mesonephric duct or tubular structures in the cervix are included in this discussion as they may simulate true adenomas of the cervix. In our material cervical adenomas have been rare while adenosis has been relatively frequent. The 4 adenomas arising in a predominantly fibrous or muscular stroma have been de-

We have examined 59 cases of adenosis of the endocervical glands. This figure does not include all the cases in the department as a number have been entered under the diagnosis of chronic cervicitis. Similar conditions have been described in the literature under a variety of terms including cystadenoma, proliferative adenoma, cystic adenoma, and adenomatoid hyperplasia. 74-76 Most textbooks of pathology describe this condition and its inflammatory background. Appelberg 77 has discussed an inflammatory condition of the cervix not unlike adenosis of the endocervical glands which he called

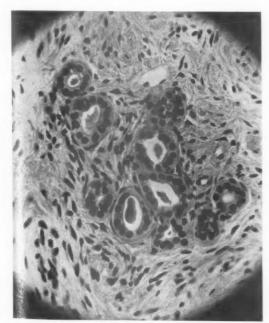


Fig. 10. Higher power magnification of Fig. 9. Close grouping of tubule-like structures with typical cuboidal epithelium. (×400; reduced approximately ½3.)

cystadenomyofibrosis. Laffont and Montpellier⁷⁸ have pointed out the need to differentiate true cervical adenomas from "alleged" adenomas or adenomatoid glandular hyperplasia. They described the latter as a hyperplasia of endocervical glandular tissue due to irritation or inflammatory causes, while the true adenoma had a property of growth without apparent inciting cause. They also noted that the adenomatoid condition would improve as the inflammatory reaction cleared, but the adenoma would show no such regressive response.

The process may be microscopic or involve the entire endocervical canal and penetrate the cervical stroma to some depth (Fig. 7). The portio of the cervix is seldom involved as in the case of Nabothian cysts. Histologically, multiple and usually parvilocular glands of the endocervical type are found. The epithelium is either columnar with basal nuclei or, more often, cuboidal or flattened because of glandular distention due to the mucinous secretion of the epithelium and obliteration of the gland ostia (Fig. 8). The glands are separated by connective tissue septa of varying degrees of thickness. The mucinous character of the epithelium can easily be demonstrated with mucicarmine or periodic acid-Schiff stains. When situated deep in the cervical stroma, it is occasionally necessary to distinguish these glands from those of mesonephric origin. This may be done with the differential stains described above, since the mesonephric structures contain no intracellular mucin. In our experience there has been no difficulty in determining the benignity of the process.

We have studied 55 specimens with mesonephric structures in the cervix and as yet have not seen a mesonephric adenoma. Cervical cysts of mesonephric origin are also rare, and the one case in this material was reported in detail by Huffman⁵ in 1948. Of the remaining 54 cases 25 contained scattered small areas of duct or tubules and were classified as mesonephric remnants. The other 29 specimens contained a definitely increased number of mesonephric structures and were interpreted as mesonephric adenosis (Fig. 9).

The embryology and histology of mesonephric structures in the cervix have been thoroughly reviewed in the literature.^{5, 79-81} The incidence of mesonephric structures in the cervix has been estimated at from less than 1 per cent to as much as 22 per cent.^{5, 79, 82, 83} Carrow, in unpublished material from this department, sectioned 100 cervices in multiple areas particularly in the lateral portions and found a 3.0 per cent incidence of mesonephric structures.

In our cases the mesonephric duct or tubules were usually in the lateral regions of the cervix; however, they occasionally were found near the endocervical canal. The epithelium of the tubules was cuboidal with pale cytoplasm and large, dark nuclei, while the stroma was made up of round or spindle cells (Fig. 10). The tubules were of similar size and in 10 cases were closely packed and somewhat suggestive of a microscopic adenoma. Occasionally, ductlike structures were seen in which the epithelium was either cuboidal like the tubules or, less often, low columnar. A basement membrane may be demonstrated about these mesomephric structures. The epithelium shows no secretory activity when stained for mucin or glycogen. The distinction between the diagnosis of mesonephric remnants and adenosis is largely arbitrary, and histologically there seems to be little difference between the two conditions. The major distinction appears to lie in the number and close grouping of the tubules in adenosis as compared to the usually few and widely scattered tubules in the case of mesonephric remnants.

Adenocarcinoma of the cervix of mesonephric origin is a rare but definite entity. Although none of the cases reported here remotely suggested malignancy, it is interesting to speculate on the possibility that adenosis or adenomatoid hyperplasia is a precursor of mesonephric adenocarcinoma. We have at least one case in our files in which this seems probable.

Rare and unusual cervical tumors. None

of the cases reported below is from material in our department, but we thought it to be of some interest to comment on these unusual case reports found in the literature.

Sebaceous glands have been reported to occur in the cervix.⁸⁴⁻⁸⁸ Novak⁸⁸ stated that sebaceous glands are encountered in the cervix as a result of rare segmental anomalies of the cervical epithelium. We have had the opportunity to study the case reported by Dougherty,⁸⁵ and it is difficult to say whether this is a sebaceous gland or an unusual form of metaplasia in an endocervical gland. Certainly metaplastic changes in endocervical glands are seen which are quite similar to isolated sebaceous glands.

Neurofibroma of the cervix has been described in a patient with generalized neurofibromatosis. ⁸⁹ It was composed of interlacing strands of fibrous tissue, axons, and Schwann cells.

A ganglioneuroma which had the form of a polypoid cervical tumor has been reported.⁹⁰ It was composed of Schwann cells, ganglion cells, and nerve fibers which in some cases were medullated, and the tumor was believed to have originated in the uterocervical plexus of Frankenhäuser.

Diphtheria of the cervix has ben noted. The authors could find no other case in the literature, although a number of instances of vaginal diphtheria have been cited. The cervical lesion was an extensive, proliferative, white, membranous tumefaction that was firmly adherent. Culture was positive for Corynebacterium diphtheriae, and the lesion eventually disappeared after the patient had been treated with diphtheria antitoxin.

Infectious mononucleosis associated with a tumor of the cervix has been described. The lesion was a sloughing, fungating mass which on biopsy was described as an anaplastic carcinoma of the cervix. A second biopsy, after the diagnosis of mononucleosis had been made and the systemic effects of the disease had cleared, revealed only a sulsiding inflammatory reaction. Six months later the cervix was entirely normal.

Schistosomiasis of the cervix is uncommon

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in the United States, but is not unusual in he West Indies and parts of Africa. A number of such cases have been reported.93, 94 The lesions were papilliferous or simple polypoid structures containing bilharzial pseudotubercles. Frequently, the lesions were suggestive of carcinoma and the above authors have stated that the tumors may be premalignant.

Mucocele of the cervix has been described following subtotal hysterectomy.95, 96 In each case there was a large, cystic mass which contained squamous and endocervical epithelium and glands.

Finally, a cervical polyp which contained hair has been described,97 and the author attributed this to metaplasia of the epithelium to more highly differentiated appendages.

Summary

We have presented a review of the pertinent literature and our histopathologic experience with benign cervical tumors reported in this department over the last 20 vears.

The incidence of benign tumors of the cervix in our material was 4.9 per cent, and 87 per cent of these tumors were cervical polyps.

Many benign tumors of the cervix are asymptomatic or of microscopic size, and therefore the incidence with which they are found will depend to a large extent on the awareness that they may be present, the frequency with which cervical biopsy is performed, the accuracy with which cervical specimens are selected and cut, the number of sections examined, and the thoroughness of histologic examination.

Squamous papillomas and endometriosis of the cervix appear to have a higher incidence than previously suspected.

While none of these tumors seems to be premalignant and while they are rarely associated with carcinoma, microscopic examination is mandatory in order to differentiate them from the polypoid or proliferative carcinomas of the uterine cervix or fundus

We have discussed the seemingly proliferative lesions of endocervical and mesonephric origin which to some degree simulate adenomas but in the strict sense are not true tumors.

A number of rare tumors of the cervix were described which have been reported in the literature, but with which we have had no experience.

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Office examination of fresh cancer cells by interference phase microscopy

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THE study of fresh or living, unfixed and unstained cells by means of conventional microscopes has been discouraging because the fine detail in the cells appears transparent in visible light. To bring out this detail, cells are fixed and stained by methods well established through long routine usage which are the foundation of our present knowledge of histology and pathology. Because of the routine and universal use of these methods we lose sight of the fact that changes thereby are induced in the cell before evaluation and that, as has often been reiterated, our knowledge of histology and pathology is based on the study of artifacts. We do not yet know the details of the fresh unadulterated cell in health and disease.

In the past decade there has been an increasing availability and use of special types of microscopes that are particularly adapted to the examination of fresh cells.1 The Baker Interference Microscope manufactured in this country by the American Optical Company is one of these instruments and, although its primary use is to make extremely fine measurements of optical path, it is an excellent instrument for cytological examinations of fresh cells because it illuminates fine intracellular detail in vivid contrasting colors. This is phase microscopy in color and the color contrasts can be varied at will to produce almost any combination desired. The color effects are very beautiful and the visual ease with which details are seen is exceptional. Here, however, color means nothing except a change in phase between one area and another, and a change in phase is a change in thickness or in refractive index or both. This is an ideal instrument, disregarding cost, for the office examination of fresh material from the examining table.

This report concerns cytological spreads, most of which were obtained from the uterine cervix with a cotton-tipped applicator moistened in the mounting fluid. The cervical spreads were mounted either in normal saline or in 5 per cent dextrose, lactated-Ringer's solution,* covered with a glass slip, and examined in interference phase contrast with an AO Baker Interference Microscope. Since all material was fresh, unfixed, and unstained, the slides were discarded and significant details for the record were photographed on 35 mm. color film and stored as 2 by 2 inch transparencies. Figs. 1-4 were made from these color photomicrographs.

Fig. 1A. Cells from a proved case of adenocarcinoma of the endometrium obtained after curettage but before therapy. Note the lobulated outline of the cells and the fine granules in the cytoplasm. These cells were not checked for lysis. Factors: 400× double focus optics on Kodachromo Spread was mounted in normal saline.

Fig. 1B. A white cell in the same preparation. Note the granules in the cell and the similarity to the granules in Fig. 1A. Factors 1000× water immersion shearing focus option Kodachrome.

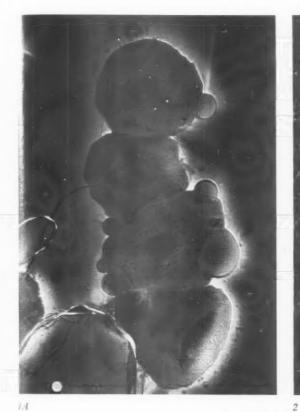
Fig. 2. Cells in sputum from a case of carcinoma of the lung before therapy. Not

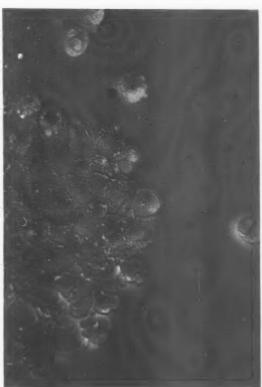
From the Department of Obstetrics and Gynecology, Jennie Edmundson Memorial Hospital.

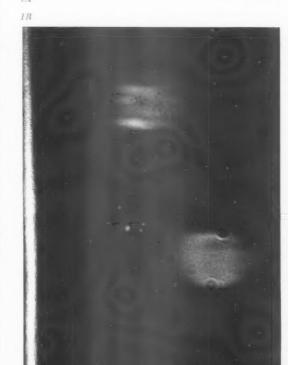
^{*}Intravenous solution No. 4127, Abbott Laboratories.

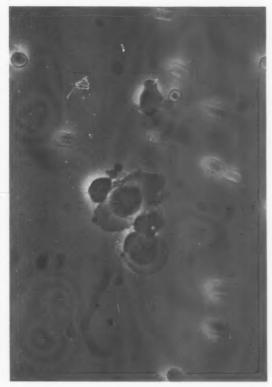
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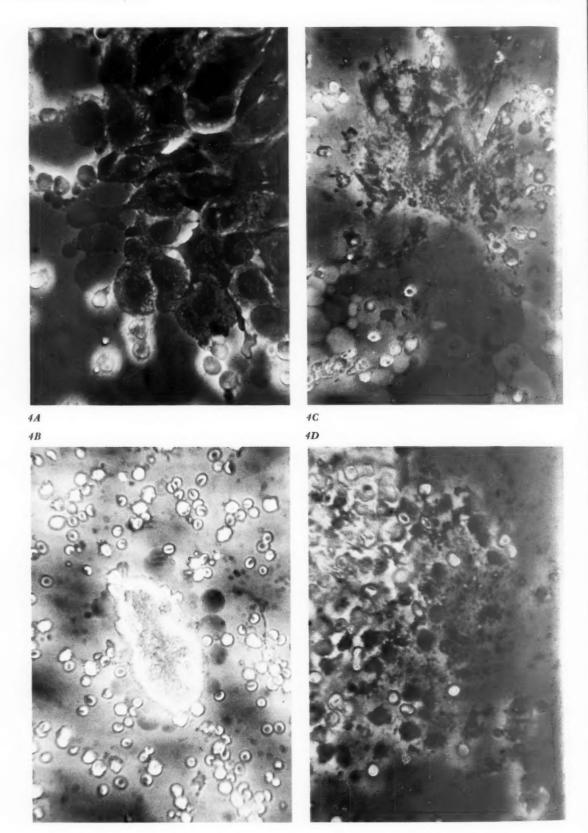
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the finger-like projections of the cancer cells. The cell at the top of the nest of cells is a white cell. These cells lysed spontaneously before additional photographs could be taken. Factors: 400x double focus optics on high speed Ektachrome. The sputum was mounted directly on a slide and examined under a cover slip.

Fig. 3. Cells from a grossly visible Stage III epidermoid carcinoma of the cervix before treatment. Note the lobulated cytoplasm of the large cell and the separating globules of cytoplasm. Other globules were seen floating free in the mounting solution. Note that the other cells in this group have decreasing amounts of cytoplasm, one nucleus appearing naked. The nuclei are large and swollen and there seem to be more granules in the nuclei with less cytoplasm. It appears that the loss of cytoplasm may be progressive. These cells lysed spontaneously after a few hours in the normal saline in which they were mounted. Since the red cells in the same preparation were not altered, it is assumed that the solution was normotonic. Factors: 400x double focus optics on high speed Ektachrome; mounted in normal saline.

Fig. 4A. A nest of cells from a case of epidermoid carcinoma of the cervix 9 months after full radiation treatment. Note the large lobules amounting to sacculations of the cytoplasm and the swollen nuclei. During the process of changing optics the cover slip was touched and the cells were sed and lost. Factors: 400x double focus optics on Superanscochrome; mounted in dextrose, Ringer-lactate solution.

Fig. 4B. A multinucleated giant cell taken from the same patient a few days later. Note the cytoplasmic lobules. Factors: 400× double focus optics on high speed Ektachrome; mounted as in Fig. 4A.

Fig. 4C. Another multinucleated giant cell in the same preparation in the process of lysing. There were several other giant cells on this slide and they all lysed spontaneously after a few hours.

Fig. 4D. A slide prepared at the same time as Fig. 4B for routine Papanicolaou stain and examination. After routine alcoholether fixation this slide was examined dry with interference phase contrast. No giant cells could be found on this slide but the area photographed appears to show the elements from a lysed giant cell but no traces of cytoplasm. The Papanicolaou report was returned negative. Factors: 400× double focus optics on high speed Ektachrome; fixed in alcohol-ether, unmounted.

Comment

All abnormal cells so far observed from proved cases of cancer have had lobulated cytoplasm and are markedly fragile as is shown by their lysing characteristics. The following tentative conclusions appear to be warranted:

- 1. Fresh cancer cells have marked and significant differences of cytoplasm from anything seen before in fixed and stained material.
- 2. Fresh cancer cells are fragile and may lyse before or on contact with fixing solutions with loss of important information.

Among others, the evidence presented raises the following questions:

- 1. Is this the true face of Cancer?
- 2. Do the swelling and lobulation of the cytoplasm and the spontaneous lysing of the cell indicate a virus effect as has been shown in cells of other organisms?
- 3. Is the dissemination of cytoplasm either by separation of lobules or by spontaneous lysis a mode of spread of the disease?

Summary

Eight photomicrographs from an interference phase microscope are presented of fresh cancer cells which show new and striking differences from cancer cells examined after fixing and staining. Fresh cancer cells are apparently fragile, lyse easily, and may be destroyed by fixing solutions.

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Factors influencing mortality rates in gynecologic malignancy

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During the past decade, vast strides have been made in the approach to gynecologic malignancy by the development of cancer detection centers, by the wider application of tests for earlier diagnosis, and by the improvement in the conventional methods of therapy. However, the consequent reduction in the mortality rates has not been as significant as we might have anticipated.

In an effort to correct this, the Committee for the Study of Pelvic Malignancy was established in 1956 under the joint auspices of the Kings County Medical Society and the Brooklyn Gynecological Society. The financial assistance of the Brooklyn Cancer Committee, Inc., was secured to defray a major portion of the expenses associated with the activation and adequate operation of the Committee. With the approval of the New York City Board of Health, the Committee for the Study of Pelvic Malignancy has undertaken to analyze the entire medical history of every patient with gynecologic cancer who dies in the Borough of Brooklyn.

The files and records of the Committee are kept confidential and certain cases are

selected for anonymous presentation and discussion at the monthly open meetings of the Committee. The medical profession in the community is invited to these meetings and encouraged to participate in the discussion of the case material. The Committee intends these sessions to be an educational experience for all practicing physicians concerned with the care of female patients, particularly those with gynecologic cancer.

In addition to holding the regular open meetings, the Committee has compiled a vast array of vital statistics following the careful analysis of the clinical material. This report is based on the analysis of 418 deaths, as listed in Table I, that occurred during the period June 1, 1956, through Dec. 31, 1957. This preliminary study indicates that the clinical result in any given case of gynecologic cancer is directly related to the stage of the disease at the time of diagnosis, the quality of the initial therapy administered, and the nature of the follow-up care rendered the patient.

Stage of the disease

The influence of the stage of the disease present at the institution of therapy upon the final outcome in a patient is illustrated for cervical cancer in Table II. The median survival of patients with Stage I cancer was 35 months; Stage II, 12 months; Stage III, 6.5 months; Stage IV, 7.5 months. It is of some interest to note in Table II that 45 per cent of the patients had Stage III or IV lesions at the time of diagnosis.

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Presented at a meeting of the Brooklyn Gynecological Society, April 15, 1959.

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The Committee's assessment of the roles played by the patient and the physician in delaying the institution of therapy from the onset of symptoms is shown in Table III. In 54 per cent of the cases, the patient consulted the physician within 3 months of the onset of symptoms. In 33 per cent there was a known delay of 4 to 48 months on the part of the patient. Contrariwise, there was no delay by the physician in 66.7 per cent of the cases. In 16.5 per cent, there was a delay of 2 to 12 months; in 16.8 per cent adequate information is not available. From a public health standpoint, the fact that 41, or 33 per cent, of the 125 patients with carcinoma of the cervix in this study were Negro merits further investigation in view of the fact that Negroes constitute only 17 per cent of the population in the community. The inadequate use of cytology in the screening of the gynecologic patients is suggested by the observation that the diagnosis of cervical cancer was established in the pathology laboratory following surgical procedures for other conditions in 5 patients. In addition, 4 patients in this group of 125 who died from cancer of the cervix had been hospitalized 10 or more years in state institutions prior to the establishment of diagnosis and the institution of therapy.

The advanced stage of the disease at the onset of therapy of those patients who died with adenocarcinoma of the uterine corpus is seen in Table IV. In only 5.1 per cent of the patients was the lesion confined to the endometrium at the time of diagnosis. Although the extent of the disease was unknown in 22.6 per cent, over two thirds of the remaining patients had advanced carcinoma on the initiation of therapy.

In analyzing the 109 cases of cancer of the body of the uterus, only 5.5 per cent were found to be in Negro patients (Table V). Another striking observation was that, whereas the median ages of the white patients with corpus cancer was 62 years, the median age of the Negro patients was only 41 years.

The Committee found it somewhat more difficult to ascertain the exact stage of dis-

Table I. Distribution of deaths due to pelvic malignancy

	Pat	ients
Site of cancer	No.	%
Ovary	165	39.5
Cervix	125	30.0
Corpus	109	26.0
Vulva	8	1.9
Vagina	5	1.2
Fallopian tubes	3	0.7
Retroperitoneum	3	0.7
Total	418	100

Table II. Relationship of survival to stage of disease in cancer of cervix

Stage of disease	Patients (%)	Median survival (months)
I	22.5	35
II	31.8	12
III	33.9	6.5
IV	11.8	7.5

Table III. Responsibility for delay and duration of delay in cancer of cervix

Duration of delay (months)	Patient delays	Physician delays (%)
0	8.3	66.7
1	20.8	
2	4.1	4.1
3	20.8	
4	4.1	4.1
5-6	8.3	
7-12	8.3	8.3
Over 12	12.5	
Unknown	12.8	16.8

Table IV. Distribution of patients according to extent of disease in adenocarcinoma of endometrium

Extent of disease	Patients (%)
Confined to endomethium	5.1
Endometrium plus cervix	3.4
Endometrium plus myometrium	17.2
Extensive	51.7
Unknown	22.6

ease in the group of 165 patients listed in Table VI with cancer of the ovary. However, inasmuch as the physician performed a total hysterectomy and bilateral salpingo-oophorectomy in only 16 per cent of the cases, it is probable that the disease was so advanced in most of the remaining 84 per cent as to preclude the carrying out of conventional therapy. It is of interest to point out the low per centage of Negro patients, namely 5.5 per cent.

Type of therapy

In evaluating the influence of therapy on the end result in a patient with gynecologic malignancy, the Committee felt that due consideration must be given to not only the quality of the therapy but also the adequacy of the patient's work-up prior to therapy. Therefore, they have recommended that a total survey of the patient be made to determine not only the patient's general status but also the extent of spread of the disease. This should include a urinalysis, blood count, blood urea and blood sugar determinations, cystoscopic and proctoscopic examinations, intravenous pyelogram, chest x-ray examination, and bone survey. Additional studies may be indicated by the findings in the particular case. Table VII shows only 50 per cent of the patients with cancer of the cervix had a complete work-up prior to therapy. In 20 per cent, only a biopsy was done and in 12 per cent the diagnosis was not even confirmed by biopsy.

Although there may be considerable variation in therapy, the Committee has prepared some recommendations to serve as a guide for what it considers adequate treatment of gynecologic malignancy. For example, in cancer of the cervix, the recommendations are related not only to the stage of the disease, but also to the experience and facilities available in the particular hospital, as follows:

Stage 0-carcinoma in situ.

A. Total hysterectomy with adequate vaginal cuff if other disease is present, if the patient is over 35, or if further child-bearing is not anticipated.

Table V. Racial and age distribution in cancer of endometrium

	Pat	ients	Median age
Race	No.	%	(years)
White	103	94.5	62
Negro	6	5.5	41

Table VI. Racial and age distribution in cancer of ovary

	Pat	ients	Median age
Race	No.	%	(years)
White	156	94.5	59
Negro	9	5.5	54

Table VII. Evaluation of pretreatment survey of patients with cancer of cervix

Work-up	Patients (%)
Complete	50
Biopsy only	20
Incomplete (but including biopsy)	12
No biopsy	12
None in hospital	6

B. Conization or amputation of the cervix if patient is in a younger age group or if further childbearing is contemplated.

C. If the uterus is not removed, periodic follow-up every 6 months to include vaginal, speculum, and rectal examinations as well as cervical smear (and biopsies if indicated by examination or smear).

Stage I or early Stage II. Choice of treatment lies between radiation therapy and radical hysterectomy with pelvic lymph node dissection. The treatment selected will depend upon such factors as the training and experience of the physician in charge, the facilities available in the hospital, and the general condition of the patient.

Late Stage II or Stage III or Stage IV. Radiation therapy. An attempt should be made to deliver 5,000 to 6,000 r to the entire pelvis during an interval of 6 weeks by combining (a) intracavitary radium in the uterus and vagina in a manner best suited for the case and (b) external radiation in which the tissue dose is accurately deter-

nined. Of the 125 patients with cancer of the cervix, 62 per cent were treated by radiation, 30 per cent by operation, and 8 per cent received no therapy.

As seen in Table VIII, of those patients treated with radiation, only 40 per cent were thought to have received complete therapy whereas 57 per cent of those undergoing operations had complete therapy. It is interesting to note in Table IX a comparison of the survival time of patients with Stage I and Stage II cancer of the cervix who received complete and incomplete therapy. Although the number of cases is not sufficient to draw conclusions of statistical significance, patients with Stage I lesions survived 45 months when they received complete therapy in contradistinction to a survival of 33 months with incomplete therapy. In Stage II, the patients with complete therapy survived 21 months; those with incomplete therapy only 10 months.

In cancer of the body of the uterus, the Committee has recommended total hysterectomy with wide vaginal cuff and bilateral salpingo-oophorectomy preceded by intrauterine radium where the uterus is enlarged to the size of 10 or more weeks' gestation or where the patient's general condition might preclude the carrying out of adequate operation. In the event radium is employed, multiple source technique is

advised. The dose is to be approximately 5,000 to 6,000 mg. hr. If spread of disease is noted at the time of operation, the patient should receive postoperative external radiation to the pelvis. Consideration should be given to the use of radium in a mold applied to the vagina postoperatively if disease is found to be present in the lower portion of the uterus. Where cervical involvement is known preoperatively, radical hysterectomy and pelvic lymph node dissection may be an alternative surgical approach.

In Table X, a significant difference is seen in the patients with adenocarcinoma of the body of the uterus who received complete and incomplete therapy. Out of a total number of 48 patients, 28, or 58 per cent, received complete therapy. The median survival in this group was 22 months. Of 42 per cent with incomplete therapy, the survival was only 5 months.

In cancer of the ovary, the Committee has recommended a total hysterectomy and bilateral salpingo-oophorectomy and omentectomy (particularly if ascites is present) when the pelvic tumor is completely resectable. If it is not possible to carry out the above procedure because of the extent of disease, the uterus should be left in place and as much tumor excised as is feasible. If the disease is limited to the pelvis, the patient should have postoperative radiation to the pelvis with a tissue dose of 3,000 to

Table VIII. Evaluation of adequacy of therapy in patients with cancer of cervix

	Ade	quate	Inade	equate	To	tal
Type of therapy	No.	%	No.	%	No.	%
Radiation	31	40	47	60	78	62
Operation	22	57	16	43	38	30
None					9	8

Table IX. Relationship of survival time to adequacy of therapy in patients with cancer of cervix

	Compl	ete therapy	Incomp	olete therapy
Stage	Patients	Median survival (months)	Patients	Median survival (months)
Stage I	- 8	45	11	33
Stage II	17	21	10	10

Table X. Relationship of survival time to adequacy of therapy in patients with cancer of endometrium

	Pat	ients	Median
Type of therapy	No.	%	survival (months)
Incomplete	28	58	22
Complete	20	42	5
Total	48	100	17

Table XI. Distribution of patients with cancer of ovary according to survival time

Survival time (months)	Patients		
	No.	%	
0-6	72	50	
7-12	31	21.4	
13-24	20	14	
25-36	6	4.2	
37-60	6	4.2	
61-120	8	5.5	
Over 120	1	0.7	

3,500 r delivered in 4 weeks. If disease is present in the upper abdomen, the patient should receive upper abdominal radiation simultaneously as tolerated. When the uterus is not removed, it may be used as a radium carrier to increase the amount of radiation delivered in the pelvis. Isotopes or nitrogen mustard may be used to control ascites or pleural effusion. Other chemotherapy may be used in the presence of persistent or recurrent disease.

Although only 16 per cent of the 165 patients with cancer of the ovary in this study received complete therapy in accord with the above recommendations, the advanced stages of disease at the time of the diagnosis may have caused such a small per cent to receive complete therapy. In comparing results in patients with complete and incomplete therapy, the Committee found that 33 per cent of those patients with complete therapy survived 2 years; whereas only 15 per cent of those with incomplete therapy survived an equivalent period. It is particularly distressing to see in Table XI that the median survival of all patients in

this series of 165 cases of cancer of the ovary was only 6 months. Table XI also shows that 123, or 85 per cent of all patients, succumbed within 24 months. At the same time, it is interesting to observe that 9 or 6 per cent survived 5 or more years.

Nature of follow-up

The Committee encountered considerable difficulty in ascertaining the exact nature of the follow-up carried out in each case. In general, they recommend that a patient with cancer should be seen every 3 months for the first year and then every 6 months if no suggestion of recurrence is found. These follow-up examinations ought to include a complete physical with pelvic examination, Papanicolaou smear, and the studies as indicated by the patient's symptoms and the findings. In a special study conducted on the cases of cancer of the cervix, the follow-up was good in 57 per cent (Table XII). In 20 per cent, the follow-up was poor; in 23 per cent, the Committee did not have sufficient information to warrant any definite statement. The experience gained in this particular analysis of the cervical cancer group suggested that a large percentage of patients with gynecologic malignancy do not have an adequate follow-up.

General principles

As a result of this analysis of 418 deaths due to gynecologic cancer and of the discussions that have transpired at the monthly open meetings, the Committee for the Study of Pelvic Malignancy believes that the following general principles may be established as an approach to the problems of gynecologic cancer.

1. A complete physical examination each

Table XII. Evaluation of posttreatment follow-up in patients with cancer of cervix

Classification	Pat	ients
of follow-up	No.	%
Good	71	57
Poor	25	20
Unknown	29	23

e

year of all female patients between the ages of 20 and 35 and a semiannual examination after the age of 35. These should include a vaginal and speculum examination and the taking of a cervical Papanicolaou smear.

2. No elective gynecologic operation should be performed prior to the recording on the patient's hospital chart of the results of a thorough pelvic examination and a cervical Papanicolaou smear. The cervical smear should have been obtained and reported within the previous 6 months.

3. Before instituting therapy for gynecologic malignancy, the physician should have made a total survey of the patient's condition to determine not only the patient's general status but also the extent of the disease. This survey should include a urinalysis, blood count, blood urea and blood sugar determination, cystoscopic and proctoscopic examinations, intravenous pyelogram, chest x-ray examination, and bone survey. Additional studies may be indicated by the findings in the particular case.

4. As a rule, extensive surgical procedures should not be performed if there is any evidence of spread of the disease beyond the confines of the pelvis. In accord with this principle, at the time of laparotomy for genital cancer, the entire abdominal contents should be explored before a definitive operation is performed.

5. Appropriate consultation both within and without the gynecologic specialty should be obtained as indicated by the requirements of the case.

Incidence of uterine malignancy in postmenopausal bleeders

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A BRIEF review of the literature reveals that there is still a wide variation in the reported incidence of uterine malignancy as a cause of postmenopausal bleeding. This discrepancy is exemplified by the figures quoted by Brewer and Miller¹ which ascribe to Zweifel² an incidence of 87 per cent malignancy among postmenopausal bleeders and to McFadyen³ an incidence of 16 per cent.

In reviewing Zweifel's paper, we find that his high incidence of cancer among post-menopausal bleeders is apparently due to the fact that he had a high percentage of patients referred to his clinic, which had a reputation for the treatment of cancer. The low incidence quoted by McFadyen is based on 100 patients with postmenopausal bleeding in whom there were 16 cancer cases. A larger sampling may have changed this result.

It is readily apparent on review of this subject that there is no universally accepted definition of a postmenopausal bleeder, and also that the selection of cases in various series may be widely different.

Brewer and Miller also emphasize the difficulties created by the various points of view of other authors as well as by an unnatural selection of the series under study. We believe that Brewer and Miller have wisely chosen to restrict their investigation to "bleeding from the uterus."

Although not desirous of adding to this confusion, we felt that a different approach

might cast further illumination on this problem.

We have reviewed the pathologic diagnosis in 2,000 women of 53 years of age and over admitted to the Royal Victoria Montreal Maternity Hospital during the past 20 years for diagnostic curettage. We chose women 53 years and over with the assumption that the large majority of these women would be postmenopausal. Sampling of 200 consecutive case histories revealed that 2 women (1 per cent were apparently still menstruating regularly and 10 women (5 per cent) were bleeding irregularly without having stopped. The remaining 188 patients (94 per cent) had had an interval of one year of absence of menstrual periods prior to their diagnostic procedure.

Women in whom there were vulvar or vaginal lesions causing bleeding were excluded unless there was an obvious concurrent lesion of the uterus which could also cause bleeding.

This series does not include pathologic specimens from major surgical procedures or vaginal repairs, whether curettage was performed as a routine procedure or not unless there existed a uterine pathologic condition directly responsible for bleeding such as endometrial cancer. In so selecting our cases on the basis of the pathology report, we feel that we are in fact analyzing a large number of postmenopausal bleeders and that the discrepancy of our method is minor and is counterbalanced by the larger volume of cases studied.

We have classified our pathologic findings

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Table I. Uterine lesions found in 2,000 diagnostic procedures

Atrophy endometrium	500 (25%)
Hyperplasia endometrium	217 (10.8%)
Endometrial polyp	274 (13.7%)
Endometritis	59 (2.9%)
Malignancy endometrium	197 (9.8%)
Cervicitis	516 (25.8%)
Cervical polyp	390 (19.5%)
Malignancy of cervix	265 (13.3%)

in broad groups, essentially separating benign from malignant lesions of both the cervix and the endometrium, as shown in Table I.

It will be noted that the total number of diagnoses in Table I exceed the number of patients because of plural lesions in the same patient. There were 462 malignant lesions of the uterus, or 23.1 per cent, in this group of 2,000 women over 53 years of age. This is an incidence of 23.1 per cent, which is close to the 27.5 per cent reported by Miller and Brewer.

Of the malignant lesions of the uterus

197 or 9.8 per cent were of the corpus and 265 or 13.3 per cent were of the cervix. This high ratio of corpus malignancy to cervix cancer is readily explained on the basis of the age selection in this group.

In conclusion, we feel that in spite of difficulties in direct comparison, our results support the lowest rather than the highest figures in the literature on the incidence of malignancy in postmenopausal bleeding. We feel that 23.1 per cent malignancy in postmenopausal bleeders is still a high figure, however, and constitutes a dangerous risk. Thus, it becomes clear that any postmenopausal bleeder necessitates a thorough investigation, for this bleeding is due to malignancy until proved the contrary.

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Combined radiologic-surgical therapy of Stage I or II carcinoma of the uterine cervix

A progress report

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CARCINOMA of the cervix is not a surgical disease. To the contrary, irradiation is the treatment of choice at the present time; but all who must care for those patients not cured by irradiation are hopeful that even more effective therapy will become available. Only long range studies of large groups of patients in carefully controlled series will show whether or not current results can be improved and, if so, how.

Several medical centers in this country and elsewhere are seeking better methods of treating carcinoma of the cervix. Some are trying to improve radiation techniques¹⁻⁶; some are evaluating the role of primary surgery⁷⁻¹⁰; others are using various combinations of irradiation and surgery¹¹⁻¹⁴; and still others are searching for reliable criteria by which the optimum of several therapies might be selected for the individual patient.¹⁵

In 1950 the Confederate Memorial Medical Center's Department of Gynecology undertook a long range study¹⁶ to answer the following questions:

1. What survival rates can be expected in patients with Stage I or II carcinoma of the

cervix if treatment consists of full therapeutic irradiation followed in 6 weeks by radical hysterectomy and bilateral pelvic lymphadenectomy?

2. What mortality and morbidity will be imposed by the performance of such an operation on the postirradiation patient?

Material

From June, 1950, through December, 1958, 105 patients with State I or II (International Classification) carcinoma of the cervix were first given adequate irradiation therapy and then subjected to radical hysterectomy and bilateral pelvic lymphadenectomy. All patients received irradiation, clinical investigation, operation, postoperative care, and follow-up studies at the Confederate Memorial Medical Center, an institution providing medical care for indigent citizens of the northern portion of Louisiana. The hospital's Tumor Clinic personnel, with the cooperation of various state agencies. have achieved 100 per cent follow-up on the patients being considered in this study.

Age distribution. The age distribution in this group of patients varies from 26 to 66 years of age. It will be noted in Table I that over 70 per cent of the patients were between 30 and 49 years old.

Race. Although the population of this

From the Department of Obstetrics and Gynecology, Confederate Memorial Medical Center.

hospital and its clinics is predominantly Negro, there is a fairly even distribution of the races in this series with 46 per cent white and 54 per cent Negro patients.

Stage. Before any therapy is instituted, the extent of disease in each patient is estimated by a member of the Department of Gynecology. The International Classification is used to establish as much uniformity as possible between this and other series. Of the 105 patients in this series 66 were judged to have Stage I and 39 to have Stage II carcinoma of the cervix. Where doubt existed as to the extent of disease, the patient was assumed to have lesser disease than suspected. Patients with carcinoma in situ are treated surgically and are not included in this series.

Histologic type of carcinoma. One hundred patients, or 95 per cent, had a histologic diagnosis of epidermoid carcinoma, while 5 had adenocarcinoma of the cervix.

Pregnancy. Three patients in this series were pregnant at the time they were found to have carcinoma of the cervix. Of these, one, who was approximately 6 weeks pregnant, had a dilatation and curettage prior to irradiation and operation; one, who was 6 months pregnant, had a hysterotomy prior to treatment; and the third patient, who was 8 months pregnant, had a cesarean section prior to therapy.

Carcinoma of the cervical stump. Five patients in this study developed carcinoma in a cervical stump. The interval between subtotal hysterectomy and the diagnosis of carcinoma varied from 2 to 12 years with an average of 5.6 years.

Methods

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In this institution all patients with a diagnosis of invasive carcinoma of the cervix proved by biopsy are referred to the Department of Radiology where they receive the appropriate external irradiation and internal radium application. During the first 4 years of this study external irradiation consisted of 2,000 r in air to each of 6 ports (about 40 per cent of the cases) and, thereafter, 3,000 r in air to each of 4 ports.

Radium therapy usually consists of the insertion of 90 mg. of radium with an Ernst applicator and leaving it in place for 72 hours for a total of 6,480 mg. hr.

Preoperative survey. Six weeks after completion of irradiation therapy, all patients under 60 years of age who were classified as having Stage I or II carcinoma at the time of original diagnosis, are considered candidates for radical hysterectomy and bilateral pelvic lymphadenectomy, provided that extensive clinical investigation reveals no contraindication to operation. This survey consists of complete history and physical examination, complete blood count, urinalysis, blood urea nitrogen, sedimentation rate, bleeding time, coagulation time, prothrombin time, chest x-ray examination, metastatic survey, barium enema, intravenous pyelography, proctoscopy, cystoscopy, electrocardiography, and 4 quadrant cervical biopsy. Additional laboratory studies and appropriate consultation are obtained as indicated.

Selection of patients. It will be noted in Table I that only 4 patients 60 years of age or older are included in this series. When this study was first begun, the available literature suggested that serious morbidity might be encountered. It was felt that any increase in survival rates that might be achieved by the combined radiologic-surgical approach would not justify the expected morbidity in patients 60 years of age or older, and they are not offered operation unless they have a radiation-resistant carcinoma or seem to be very much younger physiologically.

Except for the age limit noted above, the only patients not offered surgical procedures are those felt to be poor surgical risks, usu-

Table I. Age distribution

Age	No.	%
20-29	5	4.8
30-39	37	35.2
40-49	38	36.2
50-59	21	20.0
60-66	4	3.8
Total	105	100.0

ally as a result of chronic cardiovascular or renal disease.

Although this study was undertaken to evaluate the results of elective radical pelvic surgery in the postirradiation patient, 15 of the 105 patients in this series did not have strictly "elective" operations in that residual cancer was proved to be present in 11 by cervical biopsy and strongly suspected clinically in the other 4.

Some patients refuse preoperative studies, while others decline operation after the clinical investigation has been completed. Since the patients who decline operation receive the same irradiation therapy as the patients in this series, a comparison of the results with irradiation alone and the results with combined radiologic-surgical therapy will be the subject of a future report.

Surgery. After the clinical investigation has been completed, and if no contraindications to operation are discovered, radical hysterectomy and bilateral pelvic lymphadenectomy is carried out. The technique includes removal of the common iliac, external iliac, hypogastric, and obturator nodes, fat, and areolar tissue followed by dissection of the ureters down to their entrance into the bladder so that as much parametrial tissue as possible can be removed with the specimen. Approximately 4 cm. of vagina is removed with the specimen.

Results

At the time of this writing 105 patients with Stage I or II carcinoma of the cervix have received combined radiologic-surgical therapy. Of this number, 88, or 83.7 per cent, are now living with no evidence of disease. Survival rates for the entire series are detailed in Table II.

Five year survival rates. For purposes of comparison with other reported results, survival rates of those patients operated on 5 or more years ago are tabulated in Table III; 82.2 per cent of 28 patients who had Stage I disease and 75 per cent of 20 patients who had Stage II disease are now living and apparently free of disease for

Table II. Survival rates in patients operated on 6 months or more ago

	No.	Alive	%
Stage I			
No residual cancer	55	52	94.5
Positive specimen	8	6	75.0
Positive nodes	3	1	33.0
Total	66	59	89.4
Stage II			
No residual cancer	27	23	85.2
Positive specimen	6	4	66.7
Positive nodes	6	2	33.3
Total	39	29	74.3
Total Stages I and II			
No residual cancer	82	75	91.5
Positive specimen	14	10	71.4
Positive nodes	9	3	33.3
Total	105	88	83.7

Table III. Survival rates in patients operated on more than 5 years ago

	No.	Alive	%
Stage I			
No residual cancer	21	19	90.5
Hysterectomy specimen			
positive	5	3	60.0
Nodes positive	2	1	50.0
Total	28	23	82.2
Stage II			
No residual cancer	15	14	93.3
Hysterectomy specimen			
positive	3	1	33.3
Nodes positive	2	0	0
Total	20	15	75.0
Total Stages I and II			
No residual cancer	36	33	91.7
Hysterectomy specimen			
positive	8	4	50.0
Nodes positive	4	1	25.0
Total	48	38	79.5

periods ranging from 60 to 105 months. The over-all 5 year survival rate for this group i.e., 48 patients with Stage I or II carcinomo of the cervix, is 79.2 per cent.

Three year survival rates. The great majority of patients who succumb to recurrent disease do so within 3 years. Therefore, it is of interest to tabulate results to date or those patients operated on 3 or more years

ago, and this is done in Table IV. It will be noted that the results are practically the ame as those in Table III for 5 year survival. Eighty-three per cent of the patients who had Stage I disease and 76.7 per cent of those who had Stage II disease are alive with no evidence of disease.

Residual carcinoma and node involvement. In Tables II, III, and IV the survival rates are subdivided by Stage and further broken down to relate survival to the presence or absence of residual carcinoma in the surgical specimen or nodes. "Specimen" refers to the uterus, parametrial tissue, and vaginal cuff. When the specimen alone contains carcinoma the 5 year survival is 50 per cent, but when the nodes are involved the 5 year survival is only 25 per cent.

Table V shows that residual carcinoma was found in the surgical specimen in 12.1 per cent of the patients with Stage I disease and 15.4 per cent of the patients with Stage II disease, while the nodes were involved in 4.5 per cent of Stage I patients and 15.4 per cent of Stage II patients. Over-all, 21.9 per cent of the patients in this series were found to have residual carcinoma.

Treatment failures. Fifteen patients in this series have died, and 2 are alive but have recurrent disease. Twelve succumbed to car-

Table IV. Survival rates in patients operated on more than 36 months ago

	No.	Alive	%
Stage I			
No residual cancer	30	27	90.0
Carcinoma in specimen	8	6	75.0
Carcinoma in nodes	3	1	33.0
Total	41	34	83.0
Stage II			
No residual cancer	20	19	95.0
Carcinoma in specimen	5	3	60.0
Carcinoma in nodes	5	1	20.0
Total	30	23	76.7
Total Stages I and II			
No residual cancer	50	46	92.0
Carcinoma in specimen	13	9	69.2
Carcinoma in nodes	8	2	25.0
Total	71	57	80.2

cinoma and 3 died of intercurrent diseaseone 24 days postoperatively of pulmonary embolism, one 6 months after operation for strangulated intestinal obstruction, and one 26 months after treatment of an intracranial hemorrhage. These details are shown in Table VI.

Of the 14 patients who have had recurrence of disease, 7 developed local recurrence in the pelvis and the other 7 had distant metastases but no evidence of local recurrence.

Complications

There has been one death in the immediate postoperative period in this series of 105 patients, a primary surgical mortality of 1 per cent. This patient was an obese Negro, 60 years of age, with hypertension, cardiomegaly, and varicose veins. Because of her age and medical condition, she was not initially offered operation, but 8 weeks following completion of irradiation therapy it became apparent that she had a radiation-resistant tumor, and this was confirmed by biopsy. It was therefore necessary to carry out the surgical procedure. Twelve days later, she developed pelvic thrombophlebitis and on the twenty-fourth day after operation she had a massive pulmonary embolus and died immediately.

Late surgical mortality. One patient developed intestinal obstruction 6 months after operation. At operation she was found to have gangrenous bowel. She died soon thereafter. Autopsy revealed no evidence of carcinoma.

Genitourinary complications. By far the most common complications encountered in this series have been those involving the genitourinary tract. These have been summarized in Table VII. Seventeen patients developed pyelonephritis in the immediate postoperative period, but all responded to antibiotic therapy.

Intravenous pyelography is performed in all patients 10 to 12 days after operation. Seventeen patients had some degree of bilateral hydronephrosis, but 14 of these had normal pyelograms 3 to 6 months later and

Table V. Residual carcinoma in surgical specimen and nodes

	Stage I		Stage II		Total	
Pathology	No.	%	No.	%	No.	%
No residual carcinoma	55	83.4	27	69.2	82	78.1
Carcinoma in specimen	8	12.1	6	15.4	14	13.3
Carcinoma in nodes	3	4.5	6	15.4	9	8.6
Total	66	100.0	39	100.0	105	100.0

Table VI. Summary of treatment failures

Hospital No.	Stage	Preoperative biopsy	Surgical specimen	Pathology, nodes	Survival (months)	Cause of death
50-11131	II	-	+	-	14	Carcinoma, local recurrence
50-17629	II	-	-	+	22	Carcinoma, distant metastases
51-22853	I	~	-	-	36	Carcinoma, metastasis to liver versus primary liver disease (no autopsy)
51-25082	I		+		45	Carcinoma, local recurrence
51-31321	I	+	+	-	50	Carcinoma, distant metastases
51-32932	II	-	-	+	26	Cerebral hemorrhage
51-31322	I	_	-	+	17	Carcinoma, distant metastases
52-46044	II	+	+	rea	8	Carcinoma, local recurrence
53-55650	II	-		-	33	Carcinoma, distant metastases
53-66702	I	+	?		1	Pulmonary embolism
54-70093	II	-	+	+	3	Carcinoma, local
54-72623	II	+	+	+	2	Carcinoma, local
55-88414	I	-	+	+	13	Carcinoma, local
51-32413	I	-	-	-	6	Strangulated intestinal obstruc- tion
56-109379	II	_	-	-	30+	Alive with metastatic disease
51-26557	II	+	-	-	19+	Alive with local recurrence

required no treatment. One of the 3 who did not have spontaneous regression to normal had a left nephrostomy performed and 18 months following operation has minimal dilatation of the left collecting system and moderate dilatation of the right collecting system. Another patient has a functionless right kidney, and her most recent pyelogram shows dilatation of the left collecting system; she is now 8½ years postoperative, and a recent blood urea nitrogen determination was 24 mg. per cent. The other required a nephrostomy which functioned adequately until she died of recurrent carcinoma.

Fifteen patients had evidence of unilateral hydronephrosis in the immediate postoperative period. Eleven of these had spontaneous regression to normal, one responded to ureteral dilatations, but 3 developed unilateral asymptomatic functionless kidneys.

Thus, a total of 32 patients, or 30.5 per cent, experienced some degree of ureteral injury, but 25 had spontaneous resolution of the lesions, one responded to ureteral dilatation, and 5 patients have permanent urinary tract injuries—4 with unilateral, asymptomatic functionless kidneys and one with a permanent nephrostomy tube. At most 2 patients can be considered "urologic" cripples. So far there have been no ureterovaginal fistulas, and no patient has required a nephrectomy.

Another urinary tract complication is loss of bladder tone and excessive residual uring after voiding. An indwelling catheter is left in 72 to 96 hours following operation. The majority of patients have less than 100 c.c. of residual urine following removal of the catheter, but an occasional patient require an indwelling catheter for 2 weeks. No pa-

tient has required catheterization longer than 3 weeks.

Other complications. Complications other than genitourinary which have been met with in this series are detailed in Table VIII. The only primary surgical death occurred in one of the patients who developed thrombophlebitis. The late surgical death occurred in one of the patients who had exploratory laparotomy for intestinal obstruction.

All of the rectovaginal fistulas occurred in patients who had rather marked reactions to the irradiation therapy, and they are not thought to be a complication of the surgical procedure.

One patient accounted for several complications. She developed a left lower quadrant hematoma which became infected. It involved the left ureter and subsequently the left kidney became functionless. It also eroded into the sigmoid and resulted in a sigmoid cutaneous fistula. Attempts to drain the affected area resulted in severe injury to the left external iliac artery and the left common iliac artery had to be ligated. Fortunately, there was adequate collateral circulation to the leg.

All of the other complications listed responded to appropriate therapy and have caused no permanent damage detectable to date.

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Perhaps one day the etiology and prevention of carcinoma of the cervix will be discovered, and it can then be eliminated. Even now the tools are available to detect it early enough to achieve almost a 100 per cent cure rate. But there are still an appalling number of women who for various reasons do not receive treatment until they have rankly invasive carcinoma, and once invasion occurs the chance for cure drops sharply. Short of prevention, detection in its preinvasive stages, or discovery of an entirely new and better method of treatment, the best hope for improving the cure rates in patients with invasive carcinoma of the cervix seems to lie in careful evaluation of the various methods of treatment available today and formulation of reliable guides to select the optimum therapy for each patient.

The patients in this series are drawn entirely from an indigent population, a group who often through fear or ignorance tend to delay seeking treatment. Consequently, many of the cases of Stage I disease are almost Stage II, and many of the cases of Stage II disease are almost Stage III. To more accurately compare results of treatment with various modalities some generally acceptable method of subdividing these stages seems desirable.

Another factor which may play a part in long-term survival is the patient's nutritional status. Most of the patients in this series come from the lower socioeconomic strata.

For the time being it must be assumed that radical operation was an unnecessary

Table VII. Urinary tract complications

Complication	No.	Outcome			
Pyelonephritis	17	All responded to appro- priate antibiotic ther- apy			
Bilateral hydro nephrosis	17	 14 required no therapy and had normal pyelograms 3 to 6 months postoperatively 1 required nephrostomy which functioned satisfactorily until she died of recurrent disease 1 required left nephrostomy and now has moderate right and minimal left hydronephrosis 1 has a functionless right kidney and moderate left hydronephrosis 8½ years postoperatively 			
Unilateral hydro- nephrosis	15	11 required no therapy and had normal pyelograms 3 to 6 months postoperatively 1 required ureteral dilatations and now has normal pyelogram 3 have a functionless, asymptomatic kidney			
Vesicovaginal fistula	1	Repair attempted, but unsuccessful			

Table VIII. Other complications

Description	No.
Thrombophlebitis	4
Paralytic ileus	2
Exploratory laparotomy for intestinal obstruction (2 months to 3 years	
postoperatively)	4
Serum hepatitis	1
Pelvic hematoma	2
Wound infection	2 2
Vaginal cuff abscess	2
Atelectasis	1
Cellulitis of buttocks	1
Cellulitis of groin	1
Rectovaginal fistula	3
Sigmoid-cutaneous fistula	1
Rupture of external iliac artery	
(requiring ligation of common iliac)	1
Schizophrenic reaction	1

adjunct in those patients where pathologic examination of the tissue removed did not reveal residual carcinoma, but only long-term survival rates will show whether or not operation has benefited these patients by removing microscopic foci of carcinoma that could be found only by hundreds of serial sections or by removing cancer-prone tissue before a new carcinoma can develop.

The complications imposed by radical operation can be formidable, but, again, only time will tell whether or not they are justified.

Conclusions

1. Radical hysterectomy and bilateral pelvic lymphadenectomy can be safely performed in the patient with Stage I or II carcinoma of the cervix who has previously received full therapeutic irradiation without undue increase in mortality or prohibitive complications.

2. This series is too small and the patients have not been followed long enough for the

role of the combined radiologic-surgical approach in the treatment of patients with Stage I or II carcinoma to be evaluated, but the results so far compare favorably with those reported by other centers evaluating other methods of treatment, and they justify continued study.

Summary

Data are presented on 105 patients with Stage I or II carcinoma of the cervix treated first with full therapeutic irradiation and then 6 weeks later with radical hysterectomy and bilateral pelvic lymphadenectomy. Eighty-three and seven tenths per cent of these patients are alive without evidence of disease 6 months or more after completion of therapy. Of the 48 patients treated 5 or more years ago, 79.2 per cent are alive and apparently free of disease.

Residual carcinoma was found to be present in 21.9 per cent of the 105 patients. Fifty-six and five tenths per cent of the patients with residual carcinoma are now alive and apparently free of disease.

There has been one operative death, a primary surgical mortality of 1 per cent. In addition, one patient died 6 months after operation of intestinal obstruction.

The most common complications are those involving the genitourinary tract. The majority of these heal spontaneously, but 2 patients are "urologic" cripples.

Although the results obtained so far are favorable enough to justify continued evaluation, more time must elapse before the combined radiologic-surgical approach can be assigned its proper role in the treatment of carcinoma of the cervix.

The Radiology Department merits appreciation for their cooperation in this study.

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The combined treatment of carcinoma of the cervix with full irradiation therapy followed by radical pelvic operation

Second progress report on a series now numbering 95 cases

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Our study of combined therapy for carcinoma of the cervix was commenced in 1949 and is being made in an effort to evaluate its effectiveness as a treatment method and to learn of its place, if any, in the overall treatment of this disease.

In the first report on this series¹ we described the methods of irradiation and of operative therapy followed in the treatment of the 52 cases then reported upon, and we gave the survival results and a tabulation of the incidence and location of residual carcinoma found in the cervix, uterus, adnexa, and lymph nodes excised.

This present second report covers the 10½ year period from Jan. 1, 1949, through September, 1959, and includes 95 cases treated first by full irradiation and then by a complete radical Wertheim transabdominal excision of the upper genital tract, the broad ligaments, and the pelvic lymph nodes. There was careful pathologic study for residual carcinoma of all excised tissues. A few patients upon whom laparotomy was performed had such extensive disease—ad-

vanced Stage III or Stage IV—that we could not do the Wertheim procedure, and thus they are not included in this series. All of the operations were done by the author, assisted by two senior residents on the Gynecology Service.

As a result of our experience with this method of therapy we have come to believe that we would not elect to do this radical operation on a woman for the treatment of carcinoma of the cervix unless she had first had full irradiation therapy. We believe that the preoperative irradiation therapy permits performance of the surgical procedure with a greatly decreased chance of spreading viable cancer cells through the pelvis or the blood stream and with an increased chance of adequately "getting around" and shelling out slightly shrunken masses of cancer in the broad ligaments. Our belief is based upon the relatively high survival rate and the low recurrence rate in our series. The incidence of the common types of vaginal fistulas is still too high, but we are gradually achieving some success in our efforts to reduce it. We are upset and dismayed by the receipt of communications from physicians around the country who report, for instance, "the occurrence of ureterovaginal fistulas in 2 of 5 women on whom the operation was tried following radiation therapy"; we have urged them not

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to try the operation on any more women as it truly is difficult, even for one who has rained and worked with it for years.

Selection of cases for operation

We have striven to have the least possible selectivity enter into the formation of our series. In general we do not operate on women over 60 years of age or upon those who are extremely obese (over 200 pounds). In attempting to learn of the broad applicability of the combined method of therapy to a relatively large group of patients we have had to operate upon some hypertensive and obese women who were not very good surgical risks.

We offer and advise the operation to all women having Stage I, Stage II, and early Stage III disease provided they have had full irradiation therapy and can stand the operation; about two thirds of these women, in general, are willing to submit to the procedure, but only a few of those in the early Stage III group have been willing to undergo it.

Method of irradiation therapy

The principle of the irradiation therapy of the women in this series has been, of course, the intended delivery of a cancerocidal dose to the cervix, vaginal vault, lower uterine segment, parametrial tissues, and lateral pelvic walls. The basic plan of treatment is the same as that outlined in our first report,1 although in recent months we have been working toward delivering more of the total dose to Points A and B by deep therapy, particularly through the use of our cobalt bomb, and less by the use of implanted radium.

Preoperative studies and conditioning

The preoperative studies include the usual blood and urine examinations, chest x-ray examination, intravenous pyelograms, cystoscopy, sigmoidoscopy, a consultation by a representative of the Department of Medicine if there is any question of cardiovascular or other internal disease, and consultation by a member of the Anesthesia Department regarding the patient's acceptability as a subject for 5 to 7 hours of anesthesia. Fasting blood sugar and urea nitrogen determinations are made in nearly all cases. The patient is prepared for the operation during a 4 to 10 day period of hospitalization during which anemia is corrected by diet and the administration of iron and/or by blood transfusion, according to the blood studies and the apparent needs. She is also encouraged to eat a full, high-portein, balanced diet during this period and is given multivitamins and 600 mg. of ascorbic acid daily. She is given encouragement and emotional support by the resident in charge of the gynecology cancer service, as he directly supervises her daily care.* If she is an excessive cigarette smoker she is given sedation and is encouraged to cut down on her daily consumption to a point at which her chest clears adequately for inhalation anesthesia and her appetite for food returns adequately to permit building up her nutritional state. If her condition is poor when the disease is first diagnosed, she is admitted to the hospital and studied, built up, and supported in the same manner through the first 3 weeks, at least, of the irradiation therapy. We believe that our efforts to build up the strength of the host of the carcinoma are as important as any other category of treatment the indigent patients in our series receive.

Operative surgical therapy

The operation is practically identical to that described by Wertheim, Sampson, Bonney, and Meigs, and includes excision of all the extraperitoneal pelvic lymph nodes, the broad and cardinal ligaments, and the adnexa, uterus, cervix, and an attached skirt of the vaginal vault.1 In the last 40 cases the ureter has not been dissected from its bed in the base of the broad ligament. We do not pass ureteral catheters preopera-

*This is the National Institutes of Health Cancer Trainee, for whose services we are very grateful.

tively, since we believe this may provide added trauma to the ureters.

We leave a Foley bag bladder catheter in place for 5 to 7 days postoperatively, despite which the patient is ambulated the day after operation, being able to carry her small drainage bottle in a sling over her arm as she walks the ward. The average patient is discharged about 14 days after the operation, although we keep the elderly and hypertensive women in for about 3 weeks.

Plan of clinical staging

We have not included any Stage 0 cases in this series, believing that these noninvasive lesions are not yet carcinoma in the clinical sense. Those cases in which microscopic invasion was at all questionable, or was not agreed upon by two or three of the three examiners* of the slide, were relegated to the Stage 0 group. If there was no grossly apparent or otherwise detectable gross lesion in the cervix but definite microscopic invasion was present in the biopsy material, as attested by 3 or more qualified examiners,* the case was put in the Stage Ia group.¹

With regard to the Stage III cases, we offered the operation only to those patients in the early stage†—those in whom there was no involvement of the vagina below its middle third, no fixation and partial encirclement of the rectum, no massive extension of the broad ligament induration around posteriorly along the posterolateral bony pelvic wall to the sacrum, and no evidence of extension of the disease beyond the pelvis.

Postoperative complications

In the series of 95 cases we are reporting on, the postoperative complications of the immediate type have consisted of fever for 1 to 4 days or longer, abdominal distention, some drainage from the abdominal wound and from the vagina, and some urinary tract infections. About one quarter of the women have had one or more of these complications in the first 1 or 2 weeks after operation. The incidence of incisional drainage has been 8 per cent, and 4 women have had massive sloughing of the vaginal vault which required from 2 to 4 months to heal over. About half of the patients were given broad spectrum antibiotic therapy for 3 or 4 days before operation and for at least a week afterward. In about half the patients who were febrile in the immediate postoperative period, the fever was due to urinary tract infection, and 2 women developed evidence of acute lower ureteral obstruction for which emergency cystoscopy and catheterization of the ureters was performed. Catheters were passed over to the kidneys in both patients, the difficulty apparently having been one of edema of the lower portions of the ureters. Both women regained satisfactory ureteral drainage after cystoscopy, and their symptoms cleared up. We have not been able to detect any case in which the ureters had been ligated. In 8 women there was abdominal distention sufficient to require the passage of a long intestinal tube and continuous suction for a few days. All of the women responded well, and in no case was exploratory laparotomy for intestinal obstruction necessary in the postoperative period.

The late posttreatment complications have been vaginal fistulas, stricture of the rectum adjacent to the cervix at the level of the rectosigmoid junction, ulceration of the lower sigmoid colon with painful defecation and the passage of blood and mucus. strangury with hematuria, and frank hemorrhage from the detrusor portion of the bladder. All of these do occur after treatment by irradiation alone, but their tendency to do so is probably further enhanced by the surgical treatment. Two women had colostomy because of rectal inflammation, swelling, and stricture: in one the condition healed spontaneously; the other is awaiting excision of the strictured area and "pullthrough" of the sigmoid. One patient had

^{*}This three-person team has practically always consisted of the chief pathologist, the associate pathologist, and the author.

[†]There was one exception, a woman with advanced Stage III disease (see footnote to Table I).

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ntractable hemorrhage from the bladder 0 months after the operation, and a cystecomy was necessary. An ileal loop was attached to the vesical neck and the ureters were implanted in it.

Two women developed hydroureteronephrosis on one or both sides during the first 3 to 5 months after operation, as shown by the repeat intravenous pyelograms which are taken on patients who have urinary symptoms during this period. In both cases this condition had cleared up by the sixth postoperative month. Another woman was found, by routine preoperative intravenous pyelogram, to have an old, dead, chronic hydronephrotic right kidney, and its excision was performed 3 months after the successful Wertheim operation. Still another patient began to develop a left hydroureteronephrosis about 3 months after operation,

Table I. Postoperative vaginal fistulas in a series of 95 women who received combined therapy for carcinoma of the cervix (as of Oct. 1, 1959)

Clinical stage*			No. patier	Outcome					
	Total No. cases in series	Uretero- vaginal fistula alone	Vesico- vaginal fistula alone	Recto- vaginal fistula alone	Vesico- and recto- vaginal fistulas	Uretero- and recto- vaginal fistulas	Fistula closed sponta- neously	Fistula cured by peration	Fistula not closed
Ia	8				1				1
Ib	17			2			1		1
Ic	24	1		1	1			3	
Total	49	1		3	2		1	3	2
II	38	2	2	1	2	1	3	2	3
III (early) †		1							1
Grand total	95	4	2	4	4	1	4	5	6‡
				15					

*See Table II in the first report1 for explanation of subgroups.

†One of these cases was actually advanced Stage III: The carcinoma was undifferentiated and grew rapidly, and we operated upon the patient against our better judgment because of pressure from her husband. She died 2½ years after operation of pelvic recurrence,

‡Four of these 6 patients died, 3 of a recurrence of pelvic carcinoma. The other 2 refused further operation.

Table II. Survival results in a series of 95 women who received combined therapy for carcinoma of the cervix (as of Oct. 1, 1959)

		Patient su	rvival (including those now living and those who died)				No. patients		
	No.	10 years or more	5 years or more	4 years	3 years	Less than 3 years	with residual carcinoma*	No. patients dead	No. dead of recurrence
ia.	8	0	0	2	1	5	1	2	0
Ib	17	0	7	2	3	5	6	2	2
lc	24	0	4	3	2	15	5	3	
Total	49	0	11	7	6	25	12	7	2
II	38	0	14	1	3	20	11	5	4
III (early)†	8	0	4	1	1	2	3	2	2
Grand total	95	0	29‡	9‡	10	47	26	14	8
				9	5				

*Pathologic study of the surgical specimens revealed residual carcinoma in the cervix in 19 cases, in the uterus in 4, in the lymph nodes in 7, and in the ovary in one (5 had it at more than one site).

†See footnote to Table I. -

‡These 2 figures are counted on the basis of the fiscal years commencing January 1, hence the discrepancy with Table III.

and, despite the successful passage of a 5 F. catheter the process continued asymptomatically; 2 years after the operation the kidney was functionless and was excised. Several women who died of recurrence of the pelvic cancer had some ureteral blockage by the advancing regrowth in the late, preterminal stage of the disease.

Urinary-vaginal fistulas

Urinary-vaginal fistula is the most upsetting complication experienced by the women in our series (Table I). Although it is not a grave complication—since in our series it has never been fatal in itself nor has it been the cardinal event in a chain of events which led to a fatal result—it is a great nuisance both to the patient and to those taking care of her. Some of the women in our series have accepted the fistulas philosophically, and 2 have refused to permit an attempted surgical correction of the drainage. Others have resented the condition and have suffered emotionally from the discomfort and the urinary vaginal drainage.

Ureterovaginal fistula occurred postoperatively in 5 women in our series, vesicovaginal fistulas occurred alone in 2 cases, rectovaginal fistulas alone in 4 patients and in conjunction with a ureterovaginal fistula in 1 woman (this is included in the 5 women already mentioned), and vesicovaginal and rectovaginal fistulas occurred together in 4 more women. Thus, there were 15 patients who developed vaginal fistulas, an over-all incidence of 15 per cent.

Of the 5 women who developed a ureterovaginal fistula, one may have had it before irradiation therapy was commenced, as she had advanced Stage III disease.* A second woman developed the ureterovaginal fistula $2\frac{1}{2}$ months after operation, but it was small and it closed spontaneously 8 months postoperatively, and she is well. The third woman developed the ureteral fistula 3

months postoperatively; it did not close. stricture of the ureter gradually developed. and with it came progressive loss of renal function. The dead left kidney was removed 2 years after the Wertheim operation, by which time only slight vaginal drainage was still present; she is well. The fourth patient developed a ureterovaginal fistula 3 months postoperatively and it ceased to drain with death of the left kidney 11/2 years later; the kidney was not removed and she is well. The fifth woman had both a ureterovaginal and a rectovaginal fistula, and they drained by a sort of common cloaca into the vagina. The rectovaginal fistula was cured by first a colostomy and later a "pull-through" of the lower sigmoid down into the rectum. An ilial loop was subsequently attached to the left side of the bladder, and the left ureter was implanted in it, effectively curing the ureterovaginal fistula.

Two of these 5 women required extensive operation for cure of the ureterovaginal fistulas, but two healed spontaneously. In one woman the fistula was due principally to initial growth and regrowth of the cancer and she died of the disease 29½ months after the Wertheim operation. The occurrence of ureterovaginal fistula in 5 of the 95 women in this series, an incidence of 5 per cent, is regrettable, and we are altering our operative technique, with regard to preserving the ureteral blood supply, in an effort to eliminate it, if possible. Vesicovaginal fistulas alone occurred in two women, an incidence of 2 per cent.

Rectovaginal fistula alone occurred in 4 patients and in conjunction with ureterovaginal fistula in 1 other, an incidence of 4 per cent.

Four women had vesico- and rectovaginal fistulas, an incidence of 4 per cent. This gives a total incidence of 10 per cent for vesico- and/or rectovaginal fistulas for our series.

Of the 15 women who developed vaginal fistulas, 4 experienced spontaneous closure; this occurred in 2 of the 5 instances of ureterovaginal fistulas, in 1 of the 2 vesicovaginal fistulas, and in 1 of the 2 rectovagi-

^{*}Although we have tried not to use the operation on any women who had advanced Stage III disease, this one case was done against our better judgment because of pressure put upon us by the husband.

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nal fistulas. Five more were cured by operation. None of the remaining 6 women were rured; two of them refused further operation, and the other 4 died—3 of a recurtence of the pelvic carcinoma. In the 3 women who died of recurrence of the disease, the fistulas occurred well prior to any evidence of the recurrence of the carcinoma, and thus these fistulas represent primarily the giving of a dosage of radium to the cervix, vaginal vault, and paravaginal tissues in excess of the maximal tissue tolerances there and also the effects of the operation. They may also represent infiltration of the original carcinoma into the outer coats of the bladder and/or rectum, or at least into the vaginal walls immediately overlying them. Eleven of these 15 women with fistulas are alive and well, and it does not appear that the occurrence of posttherapy vaginal fistulas in this series is of grave prognostic significance in itself. Since ureterovaginal fistulas are of relatively rare occurrence in women who receive only irradiation therapy for cervical carcinoma, they must be ascribed primarily to the added insult of the radical operation to the lower ureters after they have already received some injury from the irradiation.

We are working to decrease the incidence of fistula and can report that only 4 of the last 45 women treated have developed them.

Two of these 4 had the ureterovaginal variety, giving it a current incidence of about 4 per cent. We still have an incidence of vesico- and rectovaginal fistulas of about 6 to 8 per cent in patients treated by irradiation alone, and we hope to decrease this through decreasing the radium dosage. The last 43 patients in our series received slightly less irradiation dosage than did the first 52, and we believe we have not suffered any decrease in cure rate as a result of this change. It is too soon to know if there has been a decrease in the number of fistulas.

Survival rates

Of the 95 women in the series (Table II), 29 have survived 5 years or more, 9 for 4 years, 10 for 3 years, and 47 for less than 3 years. Fourteen patients have died, but 4 of them first lived 5 or more years after the operation. The other 81 women are alive but some have disease (Table II). As of this writing, our follow-up contact with the 95 patients we are reporting is intact or was complete at the time of their death.

A study of those patients who had the radical operation before Sept. 1, 1954, shows there were 32 who could have survived 5 years (Table III). Twenty-four of these 32 are alive and well: 8 have died. Of the 8 women who could have lived 5 years but who now are dead, 4 first lived 5 or more

Table III. Five-year survival results in a series of 32 women whose combined therapy for carcinoma of the cervix was completed by Oct. 1, 1954 (as of Oct. 1, 1959)

Clinical stage	No.	No. patients alive	No. patients dead who lived 5 years	No. patients dead who lived less than 5 years	Total patients dead	No. having residual carcinoma	No. dying of recurrence of carcinoma
I i	0						
Ib	7	6	1		1		
I	5	3	1	1	2	1	1
Total	12	9	2	1	3	1	1
11	16	11	2	3	5	5	4
III (early)	4	4				1	
Grand total	32	24	4	4	8	7	5*
		_	28				

Two of the other 3 women died of hypertensive cardiovascular disease, one of failure, and one of a stroke, and the third died of primary adenocarcinoma of the liver. There was no evidence of pelvic carcinoma recurrence in any of the 3 women.

years before dying: thus, 28 of the 32 patients, or 87 per cent, achieved a 5 year cure. This is the 5 year survival trend for our mixed series, which is made up of 12 Stage I, 16 Stage II, and 4 Stage III cases of cervical carcinoma. This series is too small, of course, to permit the drawing from it of any valid statistical data. Since 5 of the 8 women who died did so because of a recurrence of pelvic carcinoma, and 2 of these 5 first lived 5 or more years, only 3 of the 32 women, or 9 per cent, failed to make the 5 year survival because of a recurrence of the malignant disease, which gives a corrected 5 year survival rate of 91 per cent.

Three of the 8 women in the potential 5 year survival group died of other causes: 2 of hypertensive cardiovascular disease, with a terminal "stroke," and 1 of primary adenocarcinoma of the liver at the age of 76, 5½ years after completion of the combined therapy. None of these 3 had any evidence of recurrence of the disease at the time of their death.

Six other women whose operations were performed since Sept. 1, 1954, also died. One first lived 3½ years, the second 2½ years, the third 2 years, the fourth 18 months, the fifth 9 months, and the last 7 months after

Wertheim operations. Three died of recurrence of the disease. The fourth died of heart failure 18 months after treatment this was due to hypertensive cardiovascular disease complicated by obesity and diabetes. there was no evidence of recurrence of the malignant disease at the time of death. The fifth died of extensive chronic pulmonary tuberculosis and terminal acute pericarditis. and the last one of self-starvation and final hemorrhage from sloughing tissue in the vaginal vault region. Thus, 8 of the total of 14 deaths in our series were caused by recurrent pelvic malignancy, and we wonder if this means that the operation was not sufficiently radical. Since these 8 women lived 8, 5, 31/4, 21/2, 2, 2, 11/2, and 11/2 years before they died of recurrent disease, it would seem that at least the 3 who lived 31/4 or more years must have had clinical recurrence on some basis other than inadequate surgical excision. This is only conjecture, however, as we do not know the cause of cancer, or what can contain it, cause it to die out, or be unable to prevent its rebirth in the posttreatment period in cases of this type. If incomplete excision is the causative lethal factor, one wonders why these patients did not die of recurrences within 6 to 12 months after operation.

Table IV. Irradiation therapy alone versus Wertheim operation alone versus combined therapy for carcinoma of the cervix— five year survival rates in 3 series of cases*

Method of treatment	Clinical stage of disease	No. cases in series	No. achieving absolute 5 year survival	Absolute 5 year survival rate (%)
Irradiation alone (1949 to 1951 at the	I	155	138	89.0
Radiumhemmet; quoted by	II	605	330	54.5
Kottmeier ³)	III	230	77	33.5
Radical operation alone*	I	32	25	78
(Parsons' series ²)	II†	30	20	67
	III (early)†	3	1	33
Full irradiation followed by radical op-	I	12	11	92
eration* (author's series herein re-	II	16	13	81
ported)	III (early)	4	4	100

*The number of cases in the combined therapy series is too small to bear any statistical validity, but the 65 cases in the group treated with operation alone show trends which will probably be substantiated as the series increases in size.

†These figures are adapted from Parsons' tables.

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Residual carcinoma in the surgical specimens

Residual, and apparently viable, carcinoma was found in the surgical specimens of 26 of the 95 women, an incidence of 28 per cent (Table II). In 18 women there was residual carcinoma in the cervix, and it was usually situated in the peripheral portion of the cervix and not in the canal or on the portio vaginalis. In 2 of these 18 women there was also carcinoma in the myometrium of the uterus. In 2 other women carcinoma cells were found in the lymphatics of the uterus. In 5 cases there was residual carcinoma in only one or more pelvic lymph nodes, while one woman who had it in the cervix also had it in the obturator, hypogastric, and external iliac nodes, and she survived the operation only by 2 years before she died of a recurrence of pelvic cancer. Another woman had residual carcinoma in the right ovary and left obturator lymph node, and she survived 21/2 years after operation before dying of a recurrence.

Six of the 26 patients with residual carcinoma in the surgical specimens have died, and thus 77 per cent of them are still alive.* Five of the 6 women who died did so because of recurrent carcinoma (1 of the 6 died of hypertensive cardiovascular disease), which gives a corrected survival figure of 80 per cent for those still living.* Of the 20 living women in the residual carcinoma group, 9 have survived for 4 or more years, and all those who survived the first 39 months are still alive. On the other hand, 8 of the 69 patients who had no residual carcinoma died, giving a rough survival figure to date of 87 per cent for their group.* Only 3 of these 8 who died did so of recurrent carcinoma, and thus the corrected rough survival figure for the "no residual" group is 95.6 per cent.*

Comment

When an indivdual works for 10 years trying a laborious treatment method and treats nearly a hundred cases, it might be taken for granted by some that he is an enthusiastic protagonist of this type of therapy. While we are pleased with the 5 year survival trend our series is showing, we will not know how good, or how inadequate, our treatment scheme really is until at least a hundred patients have had 5 or more years elapse since radical operation. Analysis of the data at such a time should then produce figures of statistical significance, although this is more apt to be true when 200 treated cases can be so analyzed. Furthermore, it is important that those still alive at the end of 5 and 10 years after therapy should be thoroughly checked as to their state of health and well-being, because if there is a high percentage of crippled survivors, this fact, and any others pertinent to the full assessment of the results, must be carefully weighed when the final judgment is being made.

We have had real difficulty in trying to successfully apply a standard treatment method to a large number of patients, when the very nature of the disease we are treating is such as to practically demand individualization of therapy. We have gone far enough, however, to learn that we probably do improve the survival chances in all Stage Ib, Ic, and II cases we treat and it also seems that in early Stage III cases there is an improved chance of survival.

Most will agree that the 28 per cent of women who had residual carcinoma in excised organs truly were benefited by the radical operation. Even though 5 of these 26 women ultimately died of recurrent carcinoma, all but one of the other 21 are now alive. Some may contend that in those women in whom our pathological studies failed to demonstrate residual carcinoma, the operation was not indicated and was done needlessly. We must point out, however, that 3 of these 66 women ultimately died of recurrent pelvic carcinoma and that therefore not only was the operation indicated in them, but it probably should have been more radical and more thorough.

We still have no test by which we can determine which cases should or should not

^{*}Note that these are not 5 year survival rates.

have the radical operation after irradiation therapy, and, until such a test is available, we are left with the choice of operating if and when a given patient appears to have a radioresistant carcinoma (as was the case in about 15 per cent of our patients) or when a "recurrence" is detected. Since there is no way as yet by which we can tell which patients need the operation after completion of the irradiation therapy, and since it is usually too late for operation to be effective by the time a "recurrence" is clinically detectable, the rationale for doing the operation in all Stage I, Stage II, and early Stage III cases, as we have done in this series, seems valid. The inadequacy of our present knowledge regarding the nature and true natural history of carcinoma is such that we do not know if a clinical recurrence really indicates inadequate excision in every case or if it is the "breaking down" of normal cells in the remaining epithelium under the continued influences of those "chemical imbalances" which originally caused in them the change to anaplasia.

A real difficulty in trying to learn if the combined method of therapy brings increased survival benefit is that it is difficult to find a group of patients truly comparable to ours in indigency and racial predominance with which a valid kind of comparison can be made.

Parsons' recent series² is the best one having operation alone which is available to date, and a rough comparison between his series, one treated by irradiation alone,³ and ours is shown in Table IV.

Our data continue to demonstrate that deep irradiation therapy undoubtedly kills off a good deal of the carcinoma which is metastatic in the pelvic lymph nodes. Of 86 women who had Stage Ib, Ic, II, or early III cervical carcinoma when irradiation therapy was started, only 7 were found to have residual carcinoma in the nodes, an incidence of 8 per cent. Published figures for incidences of positive nodes in patients having only radical operation would average about three times this figure in series roughly similar to ours, and so it appears

that adequate deep therapy eradicates the node carcinoma in about two thirds of the cases.

Our vaginal fistula rate is too high, and we intend further reduction of the radium dosage and an increase in deep therapy in an effort to decrease the occurrence of vesico- and rectovaginal fistulas. We are endeavoring to reduce the 5.3 per cent ureterovaginal fistula rate through a modification in our operative method of handling the uterine artery. This is simply that we dissect it out close to the cervix and divide and ligate it there. Then we dissect it entirely free from the cardinal ligament tissues and the uterine veins, working laterally toward the ureter. When we reach the branch going to the bladder, we do not divide it, but dissect it out for a short distance caudad, and then we disclose the small branch supplying the ureter and do not divide it either.* Although we pick all of the tissue off of the "top," and occasionally the "sides" of the periureteral sheath as it passes through the broad ligament, we leave its arterial blood supply alone and usually do not dissect the ureter up from its bed. In our operative experience and our pathologic studies we have not found histologically recognizable carcinoma immediately adjacent to or surrounding the ureter except in an advanced Stage III or a Stage IV case, and, in a series such as ours, in which all cases are early Stage III or of lesser disease extent, we have come to believe that complete dissection of the ureter from its bed is unnecessary as a routine procedure.

In view of our findings to date we will continue our series according to the general plan we have followed thus far. One change we expect to make, however, is to greatly reduce the amount of irradiation dosage we will give in Stage Ia cases, provided sharp knife conization of the cervix with careful pathologic study permits us to be quite cer-

^{*}This technique has been recommended for several years by Dr. Joshua W. Davies of New York City, and was presented by him in a scientific exhibit at the April 1959, meeting of the American College of Obstetrician and Gynecologists at Atlantic City, New Jersey.

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It seems that the combined therapy may prove to be an adequate method of treatment of Stage I, II, and early Stage III ases of carcinoma of the cervix. Parsons, in his recent article,2 states that he believes the Wertheim operation alone is not an adequate treatment except for Stage I and early Stage II carcinomas, and he concedes that a procedure as extensive as pelvic exenteration seems to be indicated for the treatment of advanced Stage II cases as well as for Stages III and IV, if operation is to be the only treatment. It appears, therefore, that the preoperative irradiation, as we have used it, makes possible the extension of the relative adequacy of the lesser of these two surgical procedures, the Wertheim operation, through all of the Stage II cases and the early Stage III cases as well.

Finally, we must remind the reader that combined therapy is in the experimental stage, and that the indicated treatment of cervical carcinoma today is radiation of the cervix and pelvis through the use of deep therapy and the implantation of radium or radioactive cobalt. Among the best published results from radiation therapy alone to date, in large series of cases, are those of Dr. Hans Kottmeier³ (Table IV), of the Radiumhemmet in Stockholm, and we believe that those in this country who follow his general method will obtain similar survival rates.

Summary

1. A series of 95 cases of carcinoma of the cervix treated first with full irradiation therapy and, in from 4 to 52 weeks following its completion, with radical Wertheim operation (with excision of the pelvic lymph nodes) is presented.

2. The operative mortality in the series is zero. The incidence of ureterovaginal fistula is 5 per cent, of vesicovaginal fistula 2 per cent, of rectovaginal fistula 4 per cent, and of combined vesico- and rectovaginal fistula 4 per cent. The fistulas closed spontaneously in 4 women and were closed by operation in 5. In the remaining 6 women, they were not closed, and 4 of these 6 died, 3 of a recurrence of pelvic carcinoma.

3. Of the 95 patients, 14 died, 8 of a recurrence of carcinoma. The other 6 died of other diseases, and in none was there any evidence of a recurrence of the cancer at the time of death.

4. Residual carcinoma was found in the surgical specimens from 26 of the 95 women, or in 28 per cent of the cases. Five of these 26 women died of recurrent pelvic carcinoma. Three of the 69 women who had no detectable residual carcinoma in the surgical specimens also died of pelvic recurrence of the disease.

5. It appears that the radical Wertheim operation, with excision of pelvic lymph nodes, is an adequate surgical procedure (if one is to be employed following full irradiation) for the treatment of women having Stage I, Stage II, and early Stage III carcinoma of the cervix.

Our sincere thanks are due to many people who have aided and who are aiding in this study.

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Cervical carcinoma: growth and spread and some adjunctive therapeutic measures

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DESPITE the vast expenditure of time, money, and thought in past years, the survival rates for patients with invasive cervical carcinoma of a given clinical stage remains unimproved beyond a certain point, regardless of the modality of treatment. In addition, a sufficient number of unpredictable late deaths occur to render presentday standards of prognosis unreliable. There art two classic examples. One consists of those patients who eventually die from metastatic cancer within the operative field even though no histologic evidence of local disease is found at the time of radical operation. Another group develops extrapelvic spread of the malignancy, histologically identical with the initial pelvic lesion, although the primary growth is destroyed by the original treatment of either radiation or radical operation. With these concepts in mind, it is our intention to discuss some studies made by our group. Our observations with appropriate comments are considered under five headings: atypical growth preceding invasions of cervical cancer, tumor cells in the circulating blood, supportive treatment during radiation therapy, radical hysterectomy and pelvic lym-

phadenectomy without oophorectomy, and chemotherapy by perfusion.

This study encompasses the evaluation of results in a total of 505 women with invasive cervical carcinoma treated between March 1, 1949, and July 1, 1959. More than a third of these were private patients while the remainder were indigent and registered through the local tumor clinic. These women came from various sections of east Tennessee. The indigent patients were often destitute. Frequently the welfare organization of their communities had either meager or no funds to provide supportive treatment and hospitalization.

The nature of the sources from which this material was gathered allowed concurrent studies to be made only in a partial segment of the entire group of patients.

Atypical growth

Data concerning noninvasive changes with subsequent invasion of the cervical tumor were available for 3 women.

One woman was 52 years old and had postmenopausal vaginal bleeding. An examination disclosed a cervical carcinoma, classified as Schmitz Stage II. A cervical biopsy on this patient made 14 years previously was available for review. It showed carcinoma in situ.

A second woman was 29 years old when a noninvasive carcinoma was diagnosed by cone biopsy and on this basis further treat ment was refused. Six years later, when the

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patient was 35 years old, she returned with a history of an abnormal vaginal discharge of 6 months' duration. The cancer was then graded as early Schmitz Stage III.

The third patient, who was 43 years old, had a clinically clean cervix at the time of a routine physical examination but an occasional atypical cell was found in cytologic spreads from the cervical canal. Nevertheless, she disregarded the advice to have further studies made. Scant vaginal bleeding occurred 6 years and 3 months after the first examination and after 5 years of amenorrhea presumed to be menopausal. Then examination revealed a cervical carcinoma classified as early Schmitz Stage II. Circumstantial evidence indicates that this woman had incipient cancer at the time of the original examination.

Comment. Ashworth and Diddle² reviewed more than 1,800 cervical specimens that had been considered as benign tissue. Ten of these were regarded as carcinoma by hindsight.8 Six were from women later treated. Five of the 6 women still had incipient carcinoma after 5 years as determined by biopsy examination while cellular atypicalities had disappeared in the sixth patient. Graves¹⁶ indicated more than 25 years ago that it took approximately 10 vears for noninvasive carcinoma to become invasive. In 1958 Younge³⁶ reported that among untreated patients with noninvasive lesions, invasive cancer developed in 4 per cent at the end of one year, in 22 per cent after 5 years and in 33 per cent after 9 years. Other similar reports12, 35, 36 are in the interim literature. McKay and associates23 observed that atypism in the deeper layers of the squamous epithelium may precede noninvasive carcinoma. We made such an observation in one patient. Atypism, as determined by repeated cytologic and cone biopsy studies, progressed to noninvasive cancer within a period of 2.5 years.

Tumor cells in the circulating blood

Tumor cells were found in the venous blood draining the site of the invasive tumor in 8 of 35 women with cervical cancer by means of a combination of techniques employed by others.6, 21 Atypical cells were not found in blood from other sites. It is interesting that more positive smears were found in patients with endophytic than in patients with exophytic growths. Whether or not this is a coincidental relationship remains unanswered. The atypical cells were usually alone and were seldom in clumps. The advanced lesions were associated with atypical cells in the circulating blood¹⁰ more often than were the less advanced growths. Atypical cells were isolated in a subject with invasive cancer that appeared to be relatively early by clinical examination, but pathologic study showed a more advanced stage. This woman had atypical cells in the circulating blood stream a few weeks after radical operation. Whether or not this indicated the presence of a metastases is undetermined as yet. No atypical cells were found in the blood of gravid women, women without known cancer, or those with noninvasive cancer.

Comment. Thiersch³⁴ as early as 1895 observed invasion of cancerous tissue into veins. Goldmann,¹⁵ in 1897, found cancer cells not only in the venous blood of patients with advanced malignant growths but occasionally in those with early cancers.

Since 1954 Engell¹¹ and Cole and his associates⁶ published communications on the subject, mostly in relation to the gastro-intestinal tract. Recently, others^{21, 30} identified tumor cells in the circulating blood in association with many kinds of cancer, including cervical carcinoma. It is controversial as to whether or not circulating carcinomatous cells carry a dire prognosis. Cole and associates⁶ believe they do in the case of carcinoma of the colon.

It is surmised that atypical cells from the pelvic region are ordinarily filtered out of the blood as it passes through the liver and lungs. It is interesting that these are the usual sites for distant metastases in this disease. Holzaepfel and Ezell¹⁹ found that as treatment of the primary disease has improved the incidence of extrapelvic spread has increased as determined by postmortem

examination. More women live long enough to acquire distant metastases. In some of our patients the primary disease was eradicated but they died of metastatic extrapelvic disease. In retrospect, spread was established before the primary growth was destroyed. The reason that extrapelvic metastases are not more common is attributed to local tissue immunity. Moving cells do not multiply readily and fibrin is usually unavailable as a meshwork on which tumor cell may attach and propagate.

Supportive treatment

For purposes of discussion the supportive treatment is subdivided into nutrition and the prophylactic use of a wide-spectrum antibiotic.

Nutritional support. Preservation of the well-being of a patient during the time that a cancerocidal dose of radiation is given is a frequent problem. There were no reports in the literature concerning the role of nutrition in radiation therapy of cervical cancer when such a study was begun in 1949.9

The treated patients included in this part of the study can be divided into three groups: (1) (33 cases) the ill-nourished, anemic woman given nearly a 100 Gm. protein and a 2,500 calorie diet daily and appropriate antianemic measures; (2) (128 cases) the ill-nourished and anemic woman for whom no nutritional support was furnished; and (3) (258 cases) the well-nourished woman who was maintained in such a state by appropriate feeding and blood transfusion.

These things were learned: An ill-nour-ished patient, defined as one more than 10 per cent underweight, edentulous, and anemic and often with hypoproteinemia and avitaminosis is less likely than the well-nourished woman to tolerate a therapeutic course of irradiation. Adequate intake of food may make the difference between a woman's being able and not being able to complete treatment. An occasional ill-nourished patient irradiated without the benefit of supportive measures was believed to have died as a direct result of the irradi-

ation. For example, one young woman had a perforation of the small bowel at the end of therapy. The right buttock of another sloughed down to the sacral nerve. A third had a slough of the anterior portion of the abdominal wall into the rectus sheath. Three others suffered from severe enteritis. All died from the sequelae. Those either well-nourished or ill-nourished at the start and given proper supportive treatment sometimes had side reactions to the radiation but no deaths resulted from the complication. Patients with hematocrit levels that remained near normal usually recuperated within 6 weeks after treatment was completed. On the other hand, the anemic woman who did not receive supportive care required up to 6 months. The thin woman weighing less than 100 pounds suffered from visceral insufficiency more than did the larger patient. This was attributed to the greater roentgen dose to the viscera of the thin woman.

Comment. It is as important to provide proper nutritional care for the patient who is to be irradiated as it is for the woman who is to receive major surgical treatment. We instruct such a patient at the outset regarding a high-protein, high-vitamin, and high-calorie diet. The dietitian's and physician's instruction is fortified, when possible, by that of a woman who has successfully completed a course of irradiation. The last is important!

Prophylactic use of antibiotics. The next problem that concerned us was the place, if any, for the prophylactic use of a widespectrum antibiotic during radiation therapy.

A wide-spectrum antibiotic (Chloromyce-tin*), 250 mg., was given 3 times a day to 20 women with cancer during treatment and for several days after radiation was discontinued. The total amount given ranged from 22,500 to 33,750 mg. per patient. Those given the drug had less immediate skin infection, less diarrhea, and

^{*}Chloromycetin was supplied through the courtesy or Parke, Davis & Company.

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fewer urinary difficulties than the average woman treated with radiation and not given the medication. However, they eventually suffered with proctosigmoiditis in about the same proportions as did the unmedicated patients.

Comment. Animals given concomitantly a wide-spectrum antibiotic (Aureomycin) and experimental radiation to the whole body had less bacteremia from ulcerative lesions in the bowel secondary to the irradiation than did animals not given the antibiotic. Fewer of the medicated animals^{26, 27} died. Despite these apparent advantages, the routine clinical use of antibiotics during all the irradiation treatment was discontinued for several reasons. First, the prophylactic value was relatively equivocal. Second, one must reckon with the risks of side effects from the drug. Under experimental conditions epidemics caused by drug-resistant strains of bacteria could not be controlled.29 Third, the prolonged use of the wide-spectrum antibiotic is costly. Fourth, the resolution of an inflammatory process depends much upon a patient's preexistent nutritional state.

In the face of anemia, hypoproteinemia, vitamin deficiencies, and electrolyte imbalance, resistance to infection is lowered. Suppression of the bone marrow by the radiation is another stress. Antibiotics are used to control the septic component of complications. They are ineffective against aseptic factors such as thrombosis, hematoma, and necrosis of tissue, the more common complications of invasive cancer. We reserve antibiotics for those patients with wound and urinary infections or severe proctitis. Treatment is interrupted as soon as the infection is under control. If a favorable reponse is unobtained within 2 days the reatment is re-evaluated.

We do use 1.2 million units of penicillin G intramuscularly at the time of intracavitary applications of radium. Here one is packing a body orifice that drains a potentially infected cavity and precluding the issual avenue of drainage. Since the institution of this measure in 1952 only one of nearly 250 women receiving intracavitary radium had a temperature elevation to 101° F. or above orally. Prior to that time acute febrile reactions were relatively frequent under this circumstance. Not uncommonly the radium had to be removed before the desired time. It is believed, however, that a severe febrile reaction usually indicates breakthrough of the tumor into the paracervical tissues. We have never seen a patient live 5 years who had an acute febrile reaction under this circumstance.

Radical hysterectomy and pelvic lymphadenectomy without oophorectomy

Ten of 43 women selected for radical hysterectomy and pelvic lymphadenectomy were not castrated. Surgical treatment was used rather than irradiation primarily to preserve ovarian function. These women ranged from 26 to 38 years old. All were married. Each had a lesion classified as Schmitz Stage I or II. Nine of the women are well at this reporting for 1.5 to 10 years each, 6 for more than 5 years. The tenth patient was well when last seen a year after being treated. Each continued to have cyclic engorgement of the breasts. None had hot flushes; their vaginal rugae remained prominent, and cyclic, vaginal, cytologic changes continued. Unfortunately, facilities were unavailable for hormonal studies.

Comment. We confine the use of radical hysterectomy and pelvic lymphadenectomy without oophorectomy to relatively young women with lesions graded as Schmitz Stage I or II. Results under this circumstance, were comparable to those reported by McCall and associates.²² Meigs²⁴ is of the opinion that the ovaries should be conserved in young women for two reasons. One is that their removal predisposes to osteoporosis at an early age, and the other is the mental problem of castration to the patient. McCall and his associates²² summarized the literature concerning ovarian metastases in autopsy and surgical material. The chance of spread of the tumor to the ovaries was so slight as to be no hazard.

There are two questions regarding retention of the ovaries in women treated by radical hysterectomy for cervical cancer. One, does ovarian function enhance growth of residual carcinoma? Two, does removal of the uterus induce premature gonadal atrophy? With respect to the first question, Strong³³ learned that an important factor in the development of many cancers was the genetic make-up of the animal. Gardner13 believes this factor plays only a minor part in the origin of uterine cancers of mice. Whether or not it is important in the human is unknown. Cervical carcinoma has induced experimentally in mice through the administration of estrogens. 13, 14 However, treatment extended through a good part of the animal's lifetime and the drug was given in large doses. So far as known this type of experiment has not been duplicated in other animals.

Overholser and Allen²⁸ combined trauma with prolonged estrogenic therapy to produce abnormal lesions in the cervix of *Macacus rhesus* monkeys. These were interpreted at the time to be precancerous, but we are of the opinion that they are instances of benign squamous metaplasia.

There is no evidence in the literature to prove or disprove that retention of the ovaries enhances the growth of residual, cervical cancer in the human.

The clinical evidence concerning gonadal atrophy after hysterectomy is controversial and is adequately summarized elsewhere.32 Grogan and Duncan18 are the most recent proponents of oophorectomy at the time of simple hysterectomy for benign disease in women past their middle thirties. They claim that the necessity for a secondary operation and cystic changes in the retained ovaries are too common to do otherwise. On the contrary, Bancroft-Livingston,3 in a recent clinical study of a large number of women who had undergone hysterectomy, showed that these women continued to have cyclic changes in the vagina postoperatively for long periods of time, which is interpreted to mean that ovarian function continued.

Adult Macacus rhesus monkeys experimentally hysterectomized continued to have cyclic sexual skin changes. Ovulation occurs regularly as determined by repeated laparotomy. Cystic changes or atrophy of the ovary in monkeys or rats was largely dependent on disturbed ovarian blood supply or injury to the ovarian surface or both.

Based on our personal clinical and experimental experience we cannot subscribe to the idea that a total hysterectomy is usually followed by cystic changes in the gonads or loss of ovarian function provided care is taken to leave the ovarian blood supply intact, and the ovarian surface is not traumatized.

Chemotherapy by pelvic perfusion

Chemotherapy by pelvic perfusion is a new tool in the treatment of cervical cancer. So far, results are not curative. On the contrary, palliative effects are encouraging. Most of our experience concerns perfecting a technique of administration and studying side effects from the drugs used.

The segment of the body to be perfused is isolated as an extracorporeal unit. The procedure used is essentially that described by Creech and co-workers. It is possible to perfuse the extracorporeal unit with nitrogen mustard and phenylalanine in doses above that tolerated by the body as a whole. Histologic studies of the tumors usually disclose necrosis of the neoplastic cells several days after therapy is completed.

Five of 7 patients with advanced cervical cancer who were perfused are living 4 to 9 months each. A sixth patient died postoperatively of *Staphylococcus aureus* infection. The seventh died of distant metastases within a few weeks after the perfusion.

All the patients acquired leukopenia, depression of the bone marrow in the perfused part, anemia, and a drop in platelet count. These changes reached a peak 7 to 10 days postoperatively. By the middle of the third week the blood count and bone marrow showed moderate recovery. Most of the women sustained tanning of the skin over the perfused segment. One woman acquired

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motor and sensory nerve injury of some of the lumbosacral plexus. This patient received a much higher dose of nitrogen mustard than usual—four times the usual amount.

Comment. Nitrogen mustard and phenylalanine are cytotoxic substances that unite with the DNA complex of the nucleus. The duration of the activity of the drugs is not fully determined but nitrogen mustard probably is absorbed immediately by proliferating cells while phenylalanine is effective over a period of 5 to 6 hours. Presumably cancerous cells undergo mitoses more frequently than do normal cells. Therefore the former would be affected more readily than the latter. The problem is to deliver the cancerocidal agent to the neoplastic cells before they are absorbed by normal cells in the body. Experimentally, mustards are particularly neurotoxic.20

Administration chemotherapeutic of drugs is extended over a period of time with the idea that various cells are in different states of proliferation at different times. Here again our knowledge is deficient in that the life cycle of most cells is unknown. The reasons for the use of perfusion techniques are three in number: (1) to protect the liver, (2) to protect some of the bone marrow, and (3) to deliver a larger concentration of the drugs to the tumor site than can be tolerated by the body as a whole. Although the drugs are nonspecific for neoplastic cells and very toxic, they remain the most effective chemotherapeutic agents available.

Perfusion of the pelvis, as done now, requires much preparation and use of much experienced help, and it is a major procedure fraught with many potential complications. It is too early to tell whether the results will justify continued use. However, the method is ingenious and may be acceptable when the proper agent is found.

Studies with paper chromatography are being done by Rogers³¹ to learn which drugs will block or lethally disturb the metabolism of various tumors. It has been possible to clarify this situation partially for some

tumors in animals. Bacterial contamination of the specimens, so far, has precluded the few attempts made to apply this method of study to cervical cancer in the human.

Comment

Greene¹⁷ is of the opinion that a cancer is not a sudden transformation of normal cells. Instead it represents the final stage in a developmental process. During this process, the tumor may remain morphologically static but it does undergo much biologic change. The most dramatic of these is the ability to metastasize. Usually development of properties that characterize a neoplasm as malignant requires a relatively long period of time. But, in some instances, the development of malignant properties is rapid. Greene differentiates between local, contiguous, lymphatic spread and scattering of tumor by fragmentary dissemination. Based on these assumptions, it is our opinion that treatment, in the first instance, would be successful if all the neoplastic cells were removed surgically or destroyed by a cancerocidal agent. In the second instance therapy would be seldom, if ever, curative for the reason that the cancerous cells could not be destroyed without seriously injuring the host.

The spread of the growth to the lymph nodes carries a grave prognosis. The survival rates have not been modified appreciably by any combinations of treatment after distant metastases appear. Meigs²⁵ has had few patients live beyond 5 years with invasive cancer that had spread to more than one lymph node. The results of others,4, 32 also, have not been too encouraging under this circumstance. Undoubtedly many patients are incurable when first seen because they have wide dissemination of tumor cells. Some of our evidence lends support to this hypothesis. Perfusion techniques enable one to give cancerocidal agents in concentrated doses to the tumor site. At present, however, available agents are too toxic to supplant the usual modalities of treatment except for palliative purposes.

Summary

Five hundred and five women with invasive cervical carcinoma were treated during a period of 10 years and 3 months. In the course of therapy of these women some additional information was accumulated concerning atypical growth of the cervical epithelium, dissemination of cervical carcinoma, the role of nutrition, and the use of a wide-spectrum antibiotic during irradiation treatment, radical hysterectomy, and lymphadenectomy without oophorectomy, and the use of chemotherapy by pelvic perfusion.

Noninvasive carcinoma progressed to invasive cancer of the cervix in 3 patients over periods of time varying from 6 to nearly 14 years.

Epithelial neoplastic cells were identified in the circulating blood draining the tumor site of several women. Circulating atypical cells were found more frequently with the more advanced, endophytic growths than with exophytic lesions. It is hypothesized that distant metastases may arise by this route of spread.

It is important to provide nutritional care for cancerous patients during radiation treatment. Otherwise they may not be able to complete the therapy or they may succumb from complications produced by the radiation. Antibiotic therapy is used prophylactically during intracavitary radiation but not for external irradiation. It is believed that the disadvantages outweigh the advantages under the latter circumstance.

The ovaries were not removed in 10 women under 39 years old, treated by radical hysterectomy and bilateral pelvic lymphadenectomy for cervical cancer graded as International Stage I. We still consider this

procedure experimental. On the other hand it is our opinion that retention of ovarian function is not hazardous in selected patients. In the younger woman it is of physical and emotional value. If the ovarian blood supply is preserved and the surface of the ovary is uninjured, we believe that the gonads usually function normally.

Pelvic perfusion with nitrogen or phenylalanine mustard has been demonstrated to produce a radiomimetic effect on cervical cancer. However, the toxic effects of these drugs preclude their wide use.

Conclusions

We intend to leave the reader dissatisfied with the present state of knowledge about cervical carcinoma. Diagnosis is reasonably satisfactory, but better techniques are needed to offer a prognosis. The significance of identification of tumor cells in the circulating blood is still questionable. Incidentally, the procedure is laborious and requires special training for reliable results to be obtained. Supportive measures during radiation treatment reduce the morbidity and mortality effected by the radiation but only for a relatively small percentage of patients. Retention of the ovaries in young women subjected to radical pelvic operations can be applied to only a selected few.

Meanwhile utilization of other modalities of treatment, such as chemotherapy, may bring improvement when the proper agent is available.

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A family planning service in rural Puerto Rico

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EFFICIENT programming of public health services in the field of family planning requires adequate knowledge of the effectiveness of the methods of contraception to be prescribed, including the acceptance of these methods by the population concerned and suitable procedures to make the services available to couples in need of protection against unwanted pregnancy. To provide information on these points, an action type research program was conducted in Puerto Rico during the period 1949-1958 in a rural area with rugged topography and with a population of comparatively low economic and educational levels.

The site chosen was the municipio of Trujillo Alto with a population of about 13,600, according to the census of 1950. The study area borders on the metropolitan area of San Juan where a substantial minority of the local labor force is employed. A health center of the Puerto Rico Health Department and a subunit with a public health nurse in charge are situated within the study area.

In 1949 the Health Department established maternal health clinics both at the health center and at the subunit where instruction in birth control was provided on request. Supplies were made available without cost to the patient but only one type of contraceptive material was usually on hand for free distribution at any one time.

From the National Committee on Maternal Health, Inc., and the Harvard University School of Public Health.

In December, 1949, with nongovernmental funds* and under the supervision of the Johns Hopkins University School of Hygiene and Public Health, two public health nurses were added to the staff of the health center and a jeep and driver provided to facilitate access to the rural population. The work of these two nurses and of the three nurses permanently attached to the health center concerned a general health program of which family planning constituted one of several services. Contraception clinics were conducted twice weekly at the health center and once weekly at the subunit. To obtain maximum cooperation from participants, a variety of methods was presented for individual choice. These methods were: condoms, diaphragm and jelly, foam tablets, jelly with a 5 c.c. syringe, and suppositories.^{2, 3}† After examination by a physician, the patient was given a month's supply of the material she had selected. Although the nurses were prepared to give instruction in the rhythm method, no requests were made for this type of instruction. On routine home visits by the nurses, rural families were informed of the availability of family planning services. However, it was necessary for them to report to the health center or subunit for examination by a physician and for supplie.

*Including support from Youngs Rubber Corporation and Eaton Laboratories.

†The materials provided were: Fomos tablets, Koromejelly, Lactikol jelly, Lorophyn jelly, Lorophyn suppostories, Ortho-Gynol, and Preceptin. The package of Fomos recorded hydroquinone, tartaric acid, and sodium bicarbonate, and, before 1956, hydroxyquinoline sulfate. tal

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An adequate stock of materials permitting ree choice by the patient was maintained hroughout.

Because of the limited enlistment of paients, the plan was revised in November, 1954, to allow a full-time nurse to give intruction and supplies to old and new paricipants in their homes. This nurse was placed under the direction of a physician, Dr. Edris Rice-Wray, later replaced by Dr. Manuel Paniagua, of the Asociacion Puertoriqueñ pro Bienestar de la Familia, a voluntary family planning organization. The nurse made home visits to couples who were presumed to be in need of contraception services, primarily postpartum patients attending maternal health clinics. Each couple was revisited at frequent intervals, ranging from one month in the most accessible part of the study area to 3 months in the more remote sections.4 In all, 646 of the participating couples were visited in their homes and 451 received clinic service only.

Neither special facilities for sterilization nor special incentives for the utilization of existing facilities were provided in the course of the research project. Choice of sterilization as a method of birth control was made on the initiative of the participants.

During the summer of 1958 one of us (D. N. P.) visited the study area and reviewed the records of all patients who had at any time participated in the program. In addition, he interviewed in their homes all couples who were then participating in the program and obtained from them up-to-date information on their contraception practices and on pregnancies. This study is based on the data thus obtained.

Characteristics of participating couples

A total of 1,097 couples participated in the Trujillo Alto program during the period 1951-1958. This figure is close to two thirds of the number of married women 15 to 44 years of age (including those living in consensual unions) residing in the study area in

The proportion of young women 15 to 24 years of age was about twice as large among

the participating women as among married women or married mothers in the rural population of Puerto Rico. This is not surprising since among the older wives and mothers there are many who know or have reason to believe that they cannot give birth to additional children and therefore have no need to avail themselves of a contraception service. The age distribution of women participating in the project (Table I) reveals an average (mean) age of 26.2 years at the time of admission.

In spite of their youth, the participating women had experienced, on the average, 6.8 years of marital life and 3.7 pregnancies. The total number of pregnancies was 4,054, including 3,666 live births (90.4 per cent), 93 stillbirths (2.3 per cent), and 295 abor-

Table I. Age distribution of participating women, compared with the rural population of Puerto Rico, 1950

Age (years)	Participating		Rural population		
	won	nen	Married	Married	
	No.	%	women*	mothers*	
15-19	188	17.1	7.5	4.9	
20-24	410	37.4	21.4	20.7	
25-29	217	19.8	21.9	22.7	
30-34	129	11.7	18.2	19.2	
35-39	106	9.7	19.3	20.3	
40-44	47†	4.3	11.7	12.2	
Total	1,097†	100.0	100.0	100.0	

^{*}Including women living in consensual unions. †Including 10 women 45 to 49 years of age.

Table II. Years of marital life and numbers of live births experienced by participating women prior to admission.

	Partic	Participating women			
	Years of marital life	Live births	Birth rate per 1,000 marital years	lation (birth rate per 1,000 mar- ried women 1950)	
15-19	1,593	900	565	527	
20-24	2,436	1,323	543	487	
25-29	1,740	788	453	390	
30-34	1,048	430	410	306	
35-39	522	184	352	225	
40-44	129	41	318	102	
Total	7,468	3,666	491	341	

tions (7.3 per cent). The number of still-births appears plausible but the number of reported abortions—and, therefore, the total number of pregnancies—is probably too low. Only 8 women among the 1,097 had never been pregnant.

The age-specific rates of live births of the participating women prior to admission were far higher than those of the rural population of Puerto Rico as estimated for 1950 (Table II). This excess again reflects the fact that the participants were women of continuing fertility, many of whom had borne a child shortly prior to admission.

It is also of interest to compare the women participating in the Trujillo Alto program during the period 1951-1958 with a group of women seeking contraceptive advice in various communities, mainly rural, in Puerto Rico in 1937. These women, as reported in a study by Beebe and Belaval,1 had been, on the average, at a substantially more advanced stage of their reproductive careers than the women in our study. Their mean age at admission was close to 29 years, with about 10 years of marital life and 5.3 pregnancies per woman. The service instituted in Trujillo Alto was therefore more successful from the point of view of reaching younger women with many years of childbearing still before them.

The pregnancy rate experienced by the couples participating in the Trujillo Alto program after their first pregnancy, but prior to their admission to the contraception service, can be computed as 83 per 100 years of exposure compared with a rate of 86 per 100 years estimated from the data reported by Beebe and Belaval. The level of these rates is typical of those found among couples of continuing fertility, after the first pregnancy, in the absence of effective efforts at contraception.

Impact of the contraception service

The distribution of the 1,097 participating couples by status at end of observation is presented in Table III. "End of observation" is defined for respective status categories as the last visit to the couple's home in the

summer of 1958, the date of sterilization, the last reported use of contraception prior to the abandonment of all protective measures, or the last visit before the couple left the study area. Three hundred and eighty-two couples were classified as continuing contraception, including 314 couples who were active users at the last visit, having practiced contraception since the preceding visit and having accepted new supplies. Fifty-two women were pregnant at the last visit, having accidentally conceived during use of contraception while 16 couples had interrupted protective measures with the intention of having a child.

In 330 instances, one of the partners had undergone surgical sterilization. Among the great majority of these couples, the sterilization operation was performed on the wife (308), with only 22 husbands undergoing vasectomy. On the average, the wife was 27.4 years old at the time of the sterilization and had experienced 4.8 pregnancies.

A much smaller group, consisting of 74 couples, had abandoned all measures of protection.

The subtotal of 786 couples represents those who at the end of observation were still residing in the study area and were (or would have been if they had not been sterilized) in need of protection against unwanted pregnancy.

Of the remaining couples, 198 had moved away from the study area, in most cases either to the nearby metropolitan area of San Juan or to the continental United States. The residual group of 113 couples consisted of those who were no longer in need of protection because of separation, menopause, or similar reasons.

Between their admission to the contraception service and the end of observation, the 1,097 participating couples had experienced an aggregate of 31,537 months in the study area, including 748 months accounted for by 56 planned pregnancies and short periods of temporary interruption of contraception preceding them. The remainder, 30,789 months is the period of participation, comprising the 23,195 months of exposure shown in the up-

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Fable III. Participating couples, total and average months of exposure during participation and during residence in study area, number of pregnancies, and pregnancy rate per 100 years of exposure

	No. of	Months of exposure		No. of	Pregnancy	
Status at last visit	couples	Total	Average	pregnancies	rate	
During period of participation						
Contraception continued	382	11,508	30.1	294	30.7 ± 1.8	
Couples sterilized	330	5,639	17.1	366	77.9 ± 3.9	
Protection abandoned	74	981	13.3	52	63.6 ± 8.6	
Subtotal: resident and in need of pro- tection	786	18,128	23.1	712	47.1 ± 1.7	
Moved away	198	2,756	13.9	70	30.5 ± 3.6	
Others not in need of protection	113	2,311	20.5	42	21.8 ± 3.3	
Grand total	1,097	23,195	21.1	824	42.6 ± 1.5	
During period of residence in study area	ı*					
Contraception continued	382	11,508	30.1	294	30.7 ± 1.8	
Couples sterilized	330	16,562	50.2	366	26.5 ± 1.4	
Protection abandoned	74	2,550	34.5	167	78.6 ± 5.9	
Subtotal: resident and in need of pro- tection	786	30,620	39.0	827	32.4 ± 1.1	
Moved away	198	2,756	13.9	70	30.5 ± 3.6	
Others not in need of protection	113	2,311	20.5	42	21.8 ± 3.3	
Grand total	1.097	35.687	32.5	939	31.6 ± 1.0	

^{*}Including estimates for periods after sterilization or abandonment of protection (see text).

per panel of Table III and 7,594 months spent in the pregnant state, including an allowance of one month for the puerperal period.* According to the statement of the participants, contraception was practiced during 21,504 of the 23,195 months of exposure and was temporarily interrupted without the intention of achieving pregnancy during the remaining 1,691 months.

The total number of unplanned pregnancies during participation was 824. Of these, 587 occurred during a period of exposure with use of contraception and 237 during a period of nonuse. The pregnancy rate per 100 years of exposure for the entire period of participation was 42.6, according to the formula:

$$R = \frac{Pregnancies \times 1,200}{Months of exposure} = \frac{824 \times 1,200}{23,195} = 42.6 \pm 1.5 \dagger$$

The pregancy rate with use of contraception was 32.8 per 100 years of exposure, while the corresponding rate during the aggregate months of nonuse within the period of participation was 168.2. The latter very high rate suggests that most couples who interrupted contraception temporarily conceived promptly and that those who resumed contraception at all did so within a few months after delivery.

Among the couples continuing contraception at end of observation, as shown in Table III, the pregnancy rate during participation, with and without contraception, was far lower (30.7 per cent) than among those who had subsequently submitted to

†The standard error of the pregnancy rate was computed by the approximate formula:

$$S.E = \sqrt{\frac{R(1,200 - R)}{Months of exposure}}$$

^{*}The number of months spent in the pregnant and purperal state was estimated by allowing 10 months for ach live or stillbirth, 4 months for each abortion, and the elapsed number of months for each woman accidentally pregnant at end of observation. Although an allowance of one month undoubtedly falls far short of the average duration of postpartum sterility, it has been retained throughout this report in the interest of comparability with earlier studies.

sterilization (77.9 per cent) or abandoned birth control (63.6 per cent). These findings confirm the a priori reasoning that couples who practice contraception unsuccessfully tend to abandon it altogether and that those who are least successful in their efforts to prevent conception are most inclined to seek sterilization.

Couples who moved away had a pregnancy rate of 30.5 per 100 years of exposure during participation and prior to departure from the study area, roughly equaling that of couples who remained and continued contraception. The low rate of 21.8 among the residual group who no longer needed protection probably reflects the approach of menopause in a substantial proportion of these women.

Further analysis of pregnancy rates showed that poor accessibility of the home was more strongly associated with high rates both before and after admission to the service than employment of the husband in agriculture, low economic status, and a minimum of educational attainment. The pregnancy rate after admission to the service for couples without previous experience with contraception was nearly double the rate for couples with such experience.

To assess the impact of the contraception service, it is necessary to consider not only the performance of the participating couples during their period of participation, but also the effects of sterilization and of abandonment of protection.

The 330 sterilized couples experienced an estimated 10,923 months* of marital life subsequent to sterilization, during which time they were living in the study area and would

have been, without operation, in need of protection against unwanted pregnancy. The total number of months of exposure in the study area before and after sterilization was 16,562, as shown in the second part of Table III. No failures of the sterilizing operation were reported.

The 74 couples who abandoned all efforts at protection experienced 1,569 months of exposure and 1,092 months of pregnancy and puerperium in the study area after giving up birth control. The estimated number of pregnancies during this period was 115.* Months of exposure before and after abandonment of birth control totaled 2,550 with 167 pregnancies.

In summary, then, the 1,097 participating couples experienced 23,195 months of exposure during their period of participation, 10,923 months after sterilization, and 1,569 months of exposure following the abandonment of birth control. Thus, as shown in the bottom line of Table III, they were living in the study area and in need of protection for an aggregate of 35,687 months. During this period, 939 unplanned pregnancies occurred (824 during participation plus an estimated 115 after birth control had been abandoned), corresponding to a pregnancy rate of 31.6 per 100 years of exposure. This rate compares with a rate of 83 after the first pregnancy prior to admission to the contraception service.

In the same manner in which the effectiveness of the contraception service during participation can be measured by the pregnancy rate per 100 years of exposure based on the entire period of participation with and without use of contraception, the ac-

[&]quot;The following procedure was used in making the estimate: The average period elapsed between sterilization and September, 1958, was 40.5 months per couple. It was assumed that the sterilized couples were subject after sterilization to the same rate of attrition by migration from the study area and by cessation of the need for protection as were all participating couples during the period of observation, i.e., to a monthly rate of about 1.0 per 100 couples (based on 198 departures and 113 cessations of exposure in 31,537 months of observation). On this assumption, attrition amounted to 18.2 per cent of the 40.5 elapsed months per couple, leaving a residual of 33.1 months per couple, or 10,923 months for the 330 sterilized couples.

^{*}The aggregate months of marital life in the study area (2,661) was estimated by the procedure used for sterilized couples and described in the preceding footnote. The average period between abandonment of contraception and September, 1958, was 44.9 months per couple; the implied attrition by emigration from the study area and cessation of the need for protection, 19.9 per cent. Estimation of exposure months, pregnancy months, and number of pregnancies was based, somewhat arbitrarily, on the assumption that 5 per cent of the couples involved would not be able to conceive again while the remainder would experience pregnancies at the rate computed for noncontraceptor prior to admission to the service, i.e., 96 per 100 years of exposure. The resulting pregnancy rate after abandonment of birth control was 87.

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ceptance of the service can be gauged—in reverse as it were—by the incidence of sterilization and of abandonment of contraception. Since the number of couples withdrawing from participation is in part a function of the duration of their exposure to the risk of stopping, it seems appropriate to compute these rates on the same basis as was used in computing pregnancy rates, i.e., per 100 years of exposure during participation.

Analysis by socioeconomic variables reveals that a high degree of acceptance of the contraceptive service, as measured by low rates of sterilization and of abandonment per 100 years of exposure, tended to be closely associated with relatively high effectiveness, as measured by low pregnancy rates.

Couples who received instruction and supplies in their homes experienced a moderately lower pregnancy rate during participation $(40.0 \pm 1.7 \text{ per } 100 \text{ years of exposure})$ than those who had clinic service only (48.4 ± 2.8) , while the relative differences in rates of sterilization $(9.6 \pm 0.8 \text{ and } 33.6 \pm 2.3)$ and abandonment $(2.3 \pm 0.4 \text{ and } 7.1 \pm 1.1)$ were much larger. It would appear then that the provision of home visits was moderately successful in encouraging regular use of contraception and highly successful in encouraging its continuation.

Use of prescribed methods of contraception

Of the 1,097 couples participating in the Trujillo Alto program, 724 or 66 per cent accepted only one of the 5 methods of contraception offered throughout the period of their participation. Among these, 226 couples relied on jelly and syringe, 214 on the condom, 158 on the diaphragm and jelly method, 69 on suppositories, and 57 on foam lablets. Of those who tried more than one of the prescribed methods, 263 couples used two, and 110 couples three or more methods.

The condom was used by a larger number of couples than any other method (494), with jelly a close second (462). The diaphragm was used by 272 couples, suppositories by 207, and foam tablets by 166.

As stated earlier in this paper, the par-

ticipating couples practiced contraception for an aggregate of 21,504 months after their admission to the service. During these months, 587 conceptions occurred. The 5 prescribed methods, used separately, accounted for 20,716 months of exposure and 575 pregnancies. Other methods and combinations of several methods were employed during the remaining months. Of the 20,716 months of exposure with the 5 prescribed methods, 2,923 months coincided with post-partum amenorrhea.

Table IV summarizes the information obtained on the effectiveness of the 5 prescribed contraceptive methods, as practiced by the participating couples. Pregnancy rates ranged from 28.3 to 42.3 per 100 years of exposure, including postpartum amenorrhea, and from 31.9 to 50.6 per 100 years, excluding amenorrhea. These rates are similar to those reported by Beebe and Belaval, who found a rate of 29 for the diaphragm and jelly, 33 for sponge and foam powder, and 40 for jelly and syringe (including postpartum amenorrhea).

Pregnancy rates with use of condoms were significantly lower than those for all other methods combined. The ranking of the other 4 methods is suggested rather than supported by firm statistical evidence. Differences in pregnancy rates were noted between groups of couples using the various brands of jelly prescribed, but these differences were not statistically significant.

Since it is known that groups of couples in other communities have achieved pregnancy rates on the order of 5 to 10 per 100 years of exposure while using condom or diaphragm, it is clear that these two methods were employed irregularly and not according to instructions by many of the couples in Trujillo Alto. We do not know whether the incidence of omissions or of incorrect use was equally high among those who relied on jelly and syringe, foam tablets, or suppositories. It is impossible to state, therefore, that the relative positions of the 5 methods would remain the same if they were to be used by another group of couples, with greater interest in controlling fer-

Table IV. Months of exposure with prescribed methods of contraception, accidental pregnancies, and pregnancy rate per 100 years of exposure

Method of contraception	Months of exposure			Pregnancy rate		
	Including postpartum amenorrhea	Excluding postpartum amenorrhea	Accidental pregnancies	Including postpartum amenorrhea	Excluding postpartum amenorrhea	
Condom	7,963	7,071	188	28.3 ± 2.0	31.9 ± 2.4	
Diaphragm	4,355	3,757	122	33.6 ± 3.0	39.0 ± 3.5	
Jelly	4,987	4,134	150	36.1 ± 2.9	43.5 ± 3.5	
Foam tablets	1,565	1,290	50	38.3 ± 5.3	46.5 ± 6.5	
Suppositories	1.846	1.541	65	42.3 ± 5.1	50.6 ± 6.2	
All methods	20,716	17,793	575	33.3 ± 1.4	38.8 ± 1.6	

Table V. Accidental pregnancies, by method used and subsequent practice of contraception

		Subsequent practice of contraception			
Method of contraception used	Same method	Other method	Sterilization	No protection or unknown	Total
Number of pregnancies					
Condom	81	36	31	40	188
Diaphragm	55	31	16	20	122
Jelly	52	47	33	18	150
Foam tablets	15	12	14	9	50
Suppositories	12	25	10	18	65
All methods	215	151	104	105	575
Per cent distribution					
Condom	43.1	19.1	16.5	21.3	100.0
Diaphragm	45.1	25.4	13.1	16.4	100.0
Jelly	34.7	31.3	22.0	12.0	100.0
Foam tablets	30.0	24.0	28.0	18.0	100.0
Suppositories	18.5	38.4	15.4	27.7	100.0
All methods	37.4	26.2	18.1	18.3	100.0

Table VI. Couples discontinuing use of prescribed methods of contraception

	T				
Method of contraception	Change of method	Sterilization	Protection abandoned	Total*	
Number of couples disconti	inuing use				
Condom	149	97	99 .	345	
Diaphragm	83	47	47	177	
Jelly	227	77	104	408	
Foam tablets	73	25	16	114	
Suppositories	101	26	27	154	
All methods	633	272	293	1,198	
Rate of discontinuance					
Condom	22.5 ± 1.8	14.6 ± 1.5	14.9 ± 1.5	$52.0 \pm 2.$	
Diaphragm	22.9 ± 2.5	13.0 ± 1.9	13.0 ± 1.9	48.9 ± 3.	
Jelly	54.6 ± 3.6	18.5 ± 2.1	25.0 ± 2.4	98.1 ± 4.	
Foam tablets	56.0 ± 6.4	19.2 ± 3.8	12.3 ± 3.0	87.5 ± 7.	
Suppositories	65.7 ± 6.4	16.9 ± 3.3	17.6 ± 3.4	100.2 ± 7	
All methods	36.7 ± 1.4	15.8 ± 1.0	17.0 ± 1.0	69.5 ± 2.	

^{*}Excluding couples who moved away and those who discontinued contraception because they were no longer in need protection. All instances of unknown contraception practice after pregnancy classified as abandonment.

ality and more capable of carrying out their intentions.

While 539, or 94 per cent, of the couples who had accidental pregnancies stated that they had used the prescribed method "regularly," there can be no doubt that these claims were exaggerated in many instances.

What happened after the accidental pregnancies? As shown in Table V, the largest number of couples (215 or 37.4 per cent) resumed the method of contraception which they had used prior to the pregnancy, while 151 couples (26.2 per cent) switched to a different method and 104 couples (18.1 per cent) chose surgical sterilization. The residual group of 105 couples includes those who abandoned protection and those for whom the outcome is not known. Resumption of the method previously used occurred somewhat more frequently and change of method less frequently with the relatively more effective methods (condom and diaphragm) than with the other three methods.

The relative acceptance by the users of the five prescribed contraceptive methods is analyzed in Table VI. The total number of instances of discontinuance appears as 1,198. More than half of these discontinuances were changes of method, while sterilization and abandonment of protection each accounted for slightly less than one fourth. Because all instances of unknown contraceptive practice after pregnancy are classified as abandonment, this category is slightly inflated, while change of method and sterilization are correspondingly understated. The number of sterilizations (272) is smaller than shown in Table III (330) because some couples were sterilized after a period of nonuse of contraception. These cases are included under the heading of abandonment, together with those of other couples who discontinued birth control temporarily without the intention of having a child, but later resumed protective measures. The number of instances of abandonment (293) is, therefore, much higher than the number of couples shown in Table III as having abandoned protective measures (74) at end of observation.

Rates of discontinuance per 100 years of use of each method including months of postpartum amenorrhea ranged from about 50 for condom and diaphragm to about 100 for jelly and for suppositories. This over-all variation results primarily from differences in the incidence of change of method, the maximum rate of change being 3 times the minimum rate, with a highly significant break between condom and diaphragm on the one hand and jelly, foam tablets, and suppositories, on the other. In regard to sterilization and abandonment of protection, the rates vary in less regular fashion and within much narrower limits. We are inclined to consider the rate of change a specific indicator of preference for a particular method, as compared with others, among couples who want to continue the practice of contraception. The rates of sterilization and of abandonment, on the other hand, reflect the acceptance or rejection of temporary contraception in general.

A comparison of Tables IV and VI reveals a close association between the pregnancy rate with each of the prescribed methods and the corresponding rates of discontinuance and particularly of change of method. One interpretation of this association is that success in preventing conception had produced confidence in the method used and thus encouraged continued reliance on it. By the reverse interpretation, dislike of a method, reflected in high rates of discontinuance and of change, leads to irregular use and a higher pregnancy rate.

Summary

1. In a rural area of Puerto Rico 1,097 couples participated in a contraception program in which condoms, diaphragm and jelly, foam tablets, jelly and syringe, and suppositories were offered.

2. Six hundred and forty-six couples received instruction and supplies in their homes, while 451 had clinic service only.

3. After their first pregnancy and prior to admission to the contraception service the pregnancy rate of the participating couples was 83 per 100 years of exposure.

4. During participation in the program, including periods of temporary interruption of contraception without the intention of having a child, the pregnancy rate was 42.6 per 100 years of exposure.

5. Three hundred and thirty couples underwent surgical sterilization after an average period of participating in the contraception program of 17.1 months, while 74 couples abandoned all efforts at protection.

6. During their entire period of residence in the study area, including the periods after sterilization or abandonment of protection, the participating couples experienced a pregnancy rate of 31.6 per 100 years of exposure.

7. A high degree of acceptance of the contraception service, as measured by low rates

of sterilization and abandonment, tended to be closely associated with relatively high effectiveness, as measured by low pregnancy rates.

8. Home visits were moderately successful in encouraging regular use of contraception and highly successful in encouraging its continuation.

9. Pregnancy rates during use of the 5 prescribed methods ranged from 28.3 to 42.3 per 100 years of exposure, with condoms offering significantly greater protection than the 4 other methods combined.

10. Acceptance, as measured by low rates of change to other methods, was far higher for the condom and diaphragm than for the three other methods.

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CURRENT OPINION

Pertinent comments

Endometriosis and hormone therapy

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Walden, Thoreau

SUCCESSFUL therapy of endometriosis with prolonged estrogen or estrogenprogestogen therapy has been reported sporadically. The patients selected are those in whom the diagnosis is fairly apparent, maintenance of fertility is desired, symptoms are not disabling, and large space-occupying lesions are absent. Failure of general acceptance of these therapeutic measures stems from the uncertainty of the pretreatment diagnosis, the subjective evaluation of results, failure of primate experimental endometrosis to regress, and concern with effects beyond the endometrial target organs of these potent, unnatural, hormonal chemicals.

On the positive side, the histologic demonstration of eventual uterine endometrial necrosis and atrophy after 10 to 12 weeks of therapy provides a plausible morphologic basis for therapy. Why the endometrium cannot maintain the hyperplasia and decidual reaction induced by synthetic estrogens or synthetic estrogen-progestogen combinations, respectively, is one of the current mysteries of endocrine gynecology. However,

recent biochemical in vitro studies of the mechanisms of estrogen action at the tissue level provide sufficient information to construct a working hypothesis to explain the induction of necrosis and atrophy and to provide an estimate of the specific requirements for successful treatment.

It is held currently that the natural estrogen, estradiol-17 beta, acts on the endometrium in a twofold manner. The initial effect is physiologic and consists of a marked increase in uterine vascularity, mediated by the local release of histamine. This influx of all of the required materials produces tissue growth by mass action. The second mechanism is biochemical and more complex. Estradiol-17 beta functions as a cofactor in specific endometrial enzyme systems involving the transfer of hydrogen ions and electrons, specifically, diphosphopyridine and triphosphopyridine nucleotide transhydrogenases. Thus, estradiol-17 beta stimulates oxidative metabolism of endometrial cells, glucolysis, and the citric acid cycle. Several substances are inhibitors of this in vitro effect of estradiol-17 beta. The most potent of these is the unnatural isomer, estradiol-17 alpha. Diethylstilbestrol and estriol also inhibit this effect of estradiol-17 beta on a quantitative basis.

With these facts in mind, we may construct the following schema for the pharmacologic effects of large doses of synthetic estrogens: initially, these substances function in two directions, inhibition of the pituitary release of FSH and stimulation of endometrial growth. The first eventually produces regression of ovarian function and marked diminution in the elaboration of estradiol-17 beta. The second effect, operating via the release mechanism, histamine endometrial hyperplasia. With the passage of time, oxidative metabolism in the endometrium fails because of the low level of estradiol-17 beta and the inhibition of what little estradiol persists by diethylstilbestrol. Necrosis and atrophy result.

The essence of the hypothesis is that the ideal therapy of endometriosis requires the production of endometrial atrophy. This in turn requires the prevention of estradiol stimulation of the endometrium. Theoretically, this could be attained by (1) blockage of the production of FSH at the pituitary level, (2) blockage of estradiol production at the ovarian level, (3) inhibition of the effect of estradiol on uterine vascularity (inhibition of histamine release), or (4) inhibition of the estradiol effect on endo-

metrial oxidative metabolism. Only the first and last of these mechanisms have any current practicality. What they seem to be telling us is that pharmacologic experiments in normal women directed toward producing prolonged reversible endometrial atrophy will bring us more rapidly to an effective and safe method of treating endometriosis medically than a host of hit-or-miss combinations used on a small number of cases of endometriosis.

Objections to this concept are many. Perhaps the readiest is that it does not explain the beneficial effect of pregnancy on endometriosis. However, it should be remembered that the decidua vera and the decidua reflexa do atrophy. The usual explanation is that they are compressed by the pressure of the growing conceptus. This concept is now untenable. Recently, the whole fetal environment-amniotic fluid and intervillus space—has been shown to be a continuous pressure system. The decidua basalis and decidua vera are exposed to identical pressures, but only the decidua vera atrophies. Does the decidua at the placental locus have a different endocrine exposure than the decidua vera or ectopic endometrium? Estriol, produced in great quantities in late pregnancy, is an inhibitor of the stimulating effects of estradiol-17 beta on endometrial oxidative metabolism, and, for want of a better hook, we hang our hat here.

The birth of Rustam

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An early account of cesarean section in Iran

RICHARD TORPIN, M.D.*
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THE famous Iranian poet Firdausi was born A.D. 940 and died A.D. 1020-1025. He is considered one of the four most renowned of this ancient civilization along with Saade 1184-1292; Rumi 1207-1273, and Hafiz 1326-1389. Hafiz and Saade were natives of Shiraz, Firdausi of Tus, and Rumi of Balkh.

In a rather turbulent period of history Firdausi spent many years in composing Shahnama (a history of kings) in 60,000 couplets. This was based upon the prose Shahnama of Abu Mansur, written a few years earlier. Arberry¹ writes in regard to this as follows: "in about 980 Firdausi addressed himself in earnest to the labour which was to occupy him some thirty years. In the interval his fortunes had changed; the Samanid dynasty moved to its close; civil war made literature an unrewarding profession. By the time Firdausi had completed his Shah-nama in its final form (circa 1010) not only had he exhausted his patrimony, but a new royal house of Turkish blood was firmly established in Transoxiana. Mahmud the Ghaznavid, a fanatical conormist, dedicated himself to the high cause f rooting out heresy and infidelity wherever they were to be found. When Firdausi presented his vast epic in praise of Zoroastrian Persia to this man, hoping for imperial bounty to repair his impoverished estate, the auspices were inexorably adverse. Mahmud, who had already proved himself a great patron of science and letters acceptable to orthodoxy, failed to recognize the merits of Firdausi's masterpiece and offered an insultingly small reward. Though the poet, in pardonable anticipation of favours to come, had prefixed a handsome panegyric to 'that prince whose like was never seen, not since the Creator created the world,' he now relieved his feelings by penning a savage satire."

The following is the English translation by E. G. Browne:

Long years this "Shahnama" I toiled to complete, That the King might award me some recompense meet,

But naught save a heart wrung with grief and despair

Did I get from those promises empty as air! Had the sire of the King been some Prince of renown.

My forehead had surely been graced by a crown! Were his mother a lady of high pedigree, In silver and gold had I stood to the knee! But, being by birth, not a prince but a boor, The praise of the noble he could not endure!

Firdausi is beloved and quoted by the Iranian people of all classes for, in addition to the beauty of his poetry he kept alive the great national spirit and he used relatively few foreign words which by his time had begun to infiltrate the language following the Moslem invasion of Mohammed in A.D. 622. At the present time approximately 30 per cent are Arabic.

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گفيارا بدرزادن رسيم

بربرون كشد كفت في برز ما روكمت مندرال وآن براوبركمت سا نرور ادر رمی عمدود يمي وده سوسين ولال ود

بهاردل اف رور زمرده مدرسون ٢

Fig. 1. Iranian script of the birth of Rustam.



Fig. 2. This plate, a copy of one in a Persian Shahnama of unknown publisher, shows Rudabeh lying on the couch with her husband Zal sitting on the floor beside the brazier in consultation with Simurgh, the magical bird, above. At the foot of the bed is Sindukht, the mother of Rudabeh.

To a foreigner one of the most interesting and entertaining accounts in literature are the adventures of a Hercules-Paul Bunyon ancient hero Rustam, who slew lions, dragons, and enemy armies with equal celerity.

One of the most moving sketches in Shahnama is the story of the birth of Rustam. It is also one of the world's earliest descriptions of cesarean section. The couplets relating this have been penned by a local Persian scribe (Bahri), of which few are left in this tegion, and the enlargement has been photographed for reproduction here (Fig. 1).

The translation is almost literal and even in its rendition into English gives the reader an insight into the beauty of this magnificent Iranian epic poetry.

Young womanhood is compared in Iranian literature to the tall and graceful, always green cypress tree in the gardens here and also to the moon, while virile masculinity is likened to a lion.

Account of the birth of Rustam*

No where in the world up to now has a cypress become pregnant.

She who was like the brightness of the Spring had become faded, and her heart was clouded with sorrow and pain.

The burden Rudabeh bore within her caused her to shed bitter tears. Her abdomen and body also had become tense and corpulent, and her rosy features yellow as saffron.

Said the mother of Rudabeh, "O my dear daughter, what has happened that you have become so yellow?"

She replied, "Day and night I am calling out, and have become so sleepless and faded that though living it is as though I were dead.

"I think it is time that I should be relieved of this burden."

You would think that what was in her abdomen was made of stone or iron. One day it happened that she fainted, and a cry rang out

^{*}From the Shahnama of Firdausi, Book 1.



Fig. 3. Photograph of a stone relief carving of mythical character Rustam Zal; at the Museum of Shiraz.

rom Zal's porch. It was Sindukht [Rudabeh's nother], who cried out and began to claw her face and tear out her scented hair.

One by one they carried the news to Zal that he leaves of the graceful cypress had faded.

Zal came to Rudabeh's bedside, heart-sore and with grief-stricken face. All the members of the household with disheveled heads and distraught faces began tearing out their hair.

Then a thought struck Zal, and as he pondered his mind became more composed. He remembered the feather of the Simurgh [a fabulous bird] and he laughed and passed on the good news to Sindukht.

He called for a brazier, on which a fire was kindled, and he burnt part of the feather.

Instantly the air became darkened, and the bird that fulfills desires flew down. It seemed like a cloud pouring out coral-like drops, soothing to the soul. [There is a play on words here, impossible to render into English, the Persian word for "coral" having two meanings.]

Zal saluted the bird and praised and appealed to it.

The Simurgh said, "Why this sadness? Why are your eyes wet with tears? Within that silver cypress of moonlike countenance there is a lion which will be famous. First make the moon-faced one drunk and relieve your mind of fear and anxiety. Then watch how an intelligent person works a spell and brings the lion out of the box. He will incise the flank of the graceful cypress so that she will not feel any pain. He will then pull out the lion cub from the flank of that moon-faced one, which will be full of blood. Afterward he will suture the incision he had made. Cast out all fear, grief, and anxiety from your mind! Then take a herb which I will tell you; mix it with milk and musk; grind all three together, and dry the mixture in the shade; apply it to the wound, and you will see that in due course she will be restored. Then place one of my feathers there, and she will be happy under my protection. You should rejoice at what have said, and thank God that He has given you so noble a tree, which may every day bring firth auspicious fruit for you. In no way be sorrowful that your fertile branch is about to bear fruit."

Having said this, the bird plucked one of its leathers from its wing, threw it down and flew up into the sky.

Zal took up the feather and went and did what the bird had said. O how strange! All the

people were watching anxiously with their eyes full of tears and weary in heart.

Tears flowed from the eyes of Sindukht, and she asked when the baby would come out of the flank.

Then there came a dexterous mobed [Zoro-astrian priest] who made the girl intoxicated with wine. Then he incised the flank without causing pain, and found the baby in its place, and pulled it out without injury. No one in the world had ever seen such a miracle.

It was a child of lion-like appearance, long of limb and pleasant to behold.

Men and women were astonished at the sight for no one had ever heard of an infant of such elephant-like proportions.

Day and night the girl slept on insensible under the influence of the wine.

Then they sutured the wound, and with drugs relieved all pain.

When she awoke she began to talk to Sindukht. They dropped gifts of gold and jewels over the mother, and offered thanks to God.

They brought the child to her, and bore him aloft like a shield. Though one day old, he looked like a year old. He was like a heap of lilies and tulips.

The graceful cypress laughed when she saw in her boy the signs of kingly majesty.

"I am relieved [rustam] of suffering," she said. So the boy was named Rustam.

Rudabeh must have survived because she appears in sequences many years later when Rustam fought a duel, unknowingly, with his own son and mortally wounded him.

In addition to the vivid details of the operation itself, this account records one of the earliest descriptions of toxemia of pregnancy. It is also a tribute to the fortitude and endurance of the Persian women exhibited daily at the present time.

Translation made by E. A. Khorramzadeh, fourth year medical student, and corrected and amplified by the Rev. Norman Sharp, Instructor in Persian Literature, University of Shiraz, and long-time student of ancient and modern Persian script.

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Medical records

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The preparation of an accurate record is essential to the proper practice of medicine. The value of this record varies with the competence of the physician and the ingenuity of the personnel preparing the material.

Attempts to record and preserve clinical data have always been hampered by delay, illegibility, and lack of organization. The problem has become worse as medical diagnostic possibilities have increased and laboratory tests have multiplied. The Standard Nomenclature of Diseases and Operations, first proposed in 1928, officially adopted by the American Medical Association in 1930 and, supported by the Commonwealth Fund, has partially alleviated the disorganization, but many problems remain.

The system still in use in most hospitals produces a bulky record—a heterogeneous accumulation of isolated data, the processing of which requires prohibitive time and effort. The material is accurate only within the limitations of our present system of assigning normal values.

The data contained in the record are inaccessible. The entire record must be read and reread to obtain pertinent information. As improved medical care becomes available to increasing numbers of people and more refined methods for measuring body function are employed, a paradoxical situation may be created—the more knowledge accumulated in records, the less available for clinical analysis.

Why do we have records? The common

uses are: (1) legal, (2) insurance, (3) future reference for readmission, (4) research, and (5) teaching. In one hospital the record room might handle 7,000 discharges a year, and, in addition, 6,000 records might be examined for insurance and legal purposes and another 2,500 for distribution to the hospital wards because of readmission. A much smaller number would be obtained for clinical research and statistical analysis. Most physicians are reluctant to embark upon a task requiring evaluation of 100 or more records. A statistically valid series must be prepared before conclusions can be drawn. Recent articles have described methods whereby the number of cases required for statistical analysis can be reduced. It is becoming impossible for the physician to evaluate carefully the increasing amount of data within a reasonable length of time.

What are the solutions to this problem? Several are available and are functioning to a limited extent. Many physicians and hospital record rooms are unaware of new developments or do not assign them high priority. Many record committees meet to solve their problems without availing themselves of the expert help needed for processing data. Modern business does not so limit itself, and management insists that experts be assigned to the problem. Competition requires progress. The medical profession should take a similar position. Physicians ought not to consider themselves experts in all fields.

A forward-looking system has been adopted by the Commission of Professional and Hospital Activities in Ann Arbor, Michigan. The records are coded in the participating hospital by the Record Room. A

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limited coding system is employed. The material is then sent to the Commission Headquarters where it is analyzed. The results are submitted to the participating hospital for further analysis and action. About 700,000 records are processed each year from 80 participating hospitals. Such data have limited value and cannot necessarily be applied to research programs, but this is a step in the right direction, and further development should be encouraged. The information already obtained has changed several concepts concerning laboratory and ancillary procedures.

The logical extension of this system includes analysis of all pertinent data on the patient's chart, which might be processed at a central location, and the information obtained distributed for further analysis and/or publication. The use of automatic computers would permit complex coding and detailed data analysis.

What is a computer and how does it interpret and analyze data? A computer is a device which receives information and performs reasonable operations. Common examples of computers in daily usage are adding machines, the dial telephone, and the abacus. Reasonable operations are those which do not question the objective meaning and truth of the original data but do determine the implications of these data. Since these reasonable operations do not depend upon the meaning of the information, calculation is extremely rapid. Information is defined as a group of symbols which have meaning. The type of symbol may vary, but its meaning remains the same. In the computer these ymbols are arrangements of physical objects or physical equipment. In the desk calculaor, for example, the physical object may be a set of wheels with ten or more teeth, and in a large electronic computer the informaion may be recorded and analyzed as a series of electrical pulses at one millionth of a second intervals. The presence or absence of a pulse in a proper location represents information.

When information is given to the machine on a card or tape and the presence of a hole

in the card is detected, the machine is known as a digital computer; for example, the telephone relay system. Another method of placing information into a machine consists of turning a dial or wheel a certain amount and allowing some part of the machine to record the total movement; for example, the speedometer in an automobile. A machine which manipulates this type of information is known as an analog computer.

How do these machines compute? An analog machine receives information and manipulates it through a series of changes in a physical sequence. For example, the number of teeth in a gear causing a particular shaft to turn at half the speed of another shaft performs division. A digital machine handles information by means of various stations, i.e., input, output, storage, calculator, and control. This information is then flashed from one unit to another much as trains are dispatched from a control tower. The calculator, in response to appropriate signals, performs the indicated operation, i.e., division. An automatic computer is a machine which employs an external source of energy and manipulates a program requiring long sequences of reasonable operations without human assistance.

The basic unit of information developed for an automatic digital computer is the binary digit, or the "bit." There are only two binary digits, 1 and 0. They may represent yes or no, a check mark (\vee) , or a cross (\times) . They may also correspond to an "on off" condition in an electrical circuit. For example, in some computers, the information is stored by utilization of a magnetic core. This is a small "doughnut" of ferromagnetic material that can be magnetized by a small current and that will retain this magnetism until it is demagnetized by a deliberate operation. In the most common application, a wire is passed through the core of this "doughnut," and a current is sent through the wire causing it to be magnetized in one direction. Since the direction of the current determines the magnetic field polarity, the core might represent a positive or negative elementthus, the binary symbol 1 may be represented

by a positive core and the symbol 0 represented by a negative core. A further refinement allows two wires to intersect within the core and causes only one half of the current necessary to magnetize the core to pass through each wire. When both wires are conducting, the core will be magnetized. This permits the use of thousands of cores but allows only the proper core to be magnetized by passing a current through to appropriate intersecting wires.

In order for the computer to solve a problem or interpret data, it must receive instructions—a sequence of instructions put into a machine is called a program. The form of the program may vary, i.e., paper tape, magnetic tape, or a stack of punch cards. Because, in the long run, the value of any technique depends upon its accuracy, the coding must be kept simple; that is, the material from the record must be easily and quickly transferable to the punch card. It is in this area that refined coding systems find their greatest challenge. To devise a coding system that, on the one hand, encompasses most of the data necessary for detailed analysis of a medical problem and, on the other, permits rapid transfer of this material to the computing device requires considerable ingenuity.

Because of the need for improved coding methods, an attempt has been made with the cooperation of the Service Bureau, a subsidiary of IBM, to devise a coding system which would permit refined data analysis.

This method includes a code for complete urinalysis, blood chemistry and indices, cytology, roentgenography, minor surgical procedures, signs and symptoms, treatment, and pathology. For example, the items listed under urine include: sugar, albumin, specific gravity, culture, etc. For each item there is a (+) and (-) situation or, in some cases, an upper and lower limit of normal. The pertinent material is taken from the hospital record and placed on a special coding sheet prepared by IBM according to a master sheet which includes the data to be analyzed and the code assigned to a particular situation. The code is then transferred to a regular

IBM card employing the key punch technique.

What factors govern the use of an automatic computer in a particular organization? Certainly the number of persons involved in computing is a factor. A substantial saving can be introduced only if the number of persons so employed is great. An organization which already employs some type of calculator obviously will benefit by the coordination of the various units. A third factor is the type and amount of computing work done. A fourth factor is the degree to which an organization can be centralized.

Analysis of these factors with respect to medicine clearly reveals that here is a large organization capable of centralization and which is now employing vast numbers of clerical "computers" in the processing and analysis of its records.

What are some of the applications of the automatic computer? The military applications are extensive and include fire control, ballistics, flight and navigation, and various training programs. In government, computers are employed to handle problems concerning the census and also to predict the outcome of elections. The field of economics and the problems of supply and demand readily submit to computer analysis. In engineering, the design of aircraft, guided missiles, control systems, etc., depends upon efficient computation. In astronomy an automatic analog computer keeps the telescope pointed properly while the astronomer observes through the eyepiece. The applications in nuclear physics, chemistry, weather forecasting, and statistics are well known.

In medicine, where multiple factor analysis is important, computers may revolutionize the diagnosis and treatment of disease. Consider the results of detailed analysis of one million deliveries with respect to length of labor, blood pressure, albuminuria, and so forth! Automatic scanning devices for reconsizing cancer tissues are being developed. A rapid check on the tissue removed at operation and comparison with acceptable standards is a part of the Professional Activities. Service now in operation. Pilot studies in

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volving certain specialties are in progress. The future is unlimited, and further development of these programs offers to the prepared mind an important challenge. Perhaps many of the present mysteries of medicine are hidden because of "tubular vision"—a limitation imposed by the present methods of recording data.

A few of the future possibilities might include the field of medical education where the use of the computer might result in more accurate information on disease. Entire examinations might be produced, corrected, and analyzed. Nationwide comparison would be simplified, and standards raised. Another application might include the study of millions of patients with communicable diseases. The offending organism, the incubation period, etc., might be studied. Trends could be predicted months or even years before the appearance of the disease.

An entirely new concept might be the study of *physiology* employing mass data. The functions of the bladder and other hollow organs governed to some extent by the laws of physics might be re-evaluated in terms of carefully manipulated data. It is not impossible to visualize a medical computing

center equipped with the latest computing devices and staffed by physicians biophysicists and biostatisticians. This organization might be responsible for obtaining, analyzing, and distributing data from medical schools and University Hospitals in addition to community hospitals maintaining standards approved by the computing center. This would undoubtedly result in fewer physicians' seeing their names in print. However, the material published would have an accuracy and applicability unknown today—quality in exchange for quantity.

Summary

The present condition of medical records is presented. Suggestions have been advanced for improvement with an explanation of the material and methods available at present and proposed for the future.

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Reviews | Abstracts

Edited by LOUIS M. HELLMAN, M.D.

Selected abstracts

British Medical Journal

June 4, 1960.

*Roberts, D. W. T., and Haines, M.: Is There a Stein-Leventhal Syndrome? p. 1709.

Roberts and Haines: Is There a Stein-Leventhal Syndrome? p. 1709.

An evaluation of the findings in patients at the Chelsea Hospital for Women reveal differences which are held to be incompatible with Stein-Leventhal syndrome. The clinical features are correlated with the histological findings in two groups, while a third group acts as a control. Group I, typical histology and clinical syndrome of infertility, irregular periods, and hirsutism. Group II, typical histology and clinical syndrome and corpus luteum. Group III, controls; patients in the same age group, seen during the same period of time, but with varying indications for operation. All histological preparations were examined "blind" with no indications of the group to which the case belonged. Hyperplasia of the theca interna was not present in a single case in the series, and luteinization was not a feature of any case studied. There was also no hyperplasia of the theca externa noted. Group II differs only from Group I in the presence of corpus lutei indicating recent ovulation; 50 per cent of the symptomatic patients fell into Group II although many of these patients showed a marked degree of masculinization coincidental with ovulatory menstruation. Hormone studies were carried out on 8 cases and showed no abnormal levels of 17 ketosteroids or the pituitary gonadotrophins. Endometrial biopsies in 11 cases showed no endometrium in 1 case, proliferative endometrium in 2 cases, secretory endometrium in 1 case, and cystic endometrial hyperplasia in 7 cases, as opposed to the supposed presence of early proliferative endometrium associated with the syndrome. The control group as a whole presented histological findings similar to those of Groups I and II. The histological and clinical features of the cases are discussed and the conclusion is reached that the Stein-Leventhal syndrome does not appear to be a well-defined entity.

Stuart O. Silverberg

Canadian Medical Association Journal

Vol. 83, July 9, 1960.

*Ringrose, C. A. D.: Clinical, Etiological, and Economic Aspects of Salpingitis, p. 53.

Ringrose: Clinical, Etiological, and Economic Aspects of Salpingitis, p. 53.

A retrospective survey of 78 consecutive cases of salpingitis and a prospective analysis of 22 cases was undertaken. In the prospective series, following the usual history, physical examination, and routine laboratory procedures, the following procedures were done prior to the institution of therapy: (1) an endometrial biopsy, (2) a Papanicolaou smear of the vagina and cervix, (3) a blood culture, and (4) a cervical culture (of the 78 retrospective cases, 60 were acute and 18 were interval). In the prospective series 19 were acute and 3 were interval (quiescent).

The acute cases occurred most often in the 21-30 age group while the interval cases occurred most often in the 31-40 age group. There was a greater number of Negro patients afflicted. Pregnancy wastage in this group was 34 per cent. The time of coitus prior to the onset of symptoms was usually 0 to 5 days. The day of the cycle on which symptoms began was greatest during the first 5 days of the cycle.

The clinical picture of acute salpingitis was abdominal pain plus systemic signs of infec-

^{*}These articles have been abstracted.

tion. Pelvic examination demonstrated adnexal tenderness in all 79 acute cases, masses also being present in 55. In the great majority of acute cases, a significant degree of pyuria existed. Blood cultures were uniformly unproductive. In no case in the retrospective or prospective series was the gonococcus recovered from cervical cultures or cul-de-sac cultures of tubo-ovarian masses. All organisms present are normally found in the feces.

Papanicolaou smears revealed trichomonads and inflammatory cells in the vaginal smears with a high content of fresh leukocytes in the cervical smears.

The endometrial biopsies obtained in the prospective series indicated this area to be relatively resistant to inflammation.

Chloramphenicol and a penicillin-streptomycin combination were the antibiotic agents most commonly employed and most frequently effective.

John J. Dettling

Cancer .

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Vol. 12, November-December, 1959.

*Sullivan, R. D., Miller, E., and Sikes, M. P.:
Antimetabolite-Metabolite Combination
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Cancer, p. 1248.

Sullivan, Miller, and Sikes: Antimetabolite-Metabolite Combination Cancer Chemotherapy.

Previous investigation has shown that alkylating agents, as nitrogen mustard, may, where administered intra-arterially, have regressive effects on tumors not affected by the same drug administered intravenously. However, the antimetabolite drugs were not noted to exhibit this difference when daily arterial administration of single doses was used. The postulated reason for this difference in behavior of alkylating and antimetabolite drugs is that the latter may require a longer period of in vivo activity before producing antitumor effects. This is in agreement with empirical fact.

Further investigation demonstrated that the antitumor effects of antimetabolites could be enhanced by prolonging the duration of intra-arterial infusion, but at the cost of marked systemic toxicity. The authors theorized that this systemic toxicity might be modified, without completely negating the antitumor effect, by concurrent systemic administration of the ap-

propriate metabolite. They undertook to investigate this concept, using Methotrexate (4-amino-N-methyl pteroylglutamic acid) and citrovorum factor as the antimetabolite-metabolite pair.

Eighteen patients with tumors of the head and neck were treated with intra-arterial Methotrexate infusion, and intramuscular citrovorum factor. The external carotid artery was catheterized under direct vision, and pretreatment angiograms obtained to demonstrate the arterial bed to be infused and the position of the catheter. An additional 9 patients were treated with the same drug pair, with the difference that the Methotrexate was given by continuous intravenous infusion.

Partial or complete regression of the tumor was found in 10 of the 18 patients on the intraarterial regimen, and this route yielded more dramatic and sustained regressions than did the intravenous route.

Both antitumor and general toxicity are increased tenfold or more by continuous intraarterial infusion, and, although local or systemic toxicity was noted in nearly all cases, intermittent administration of the metabolite protects the systemic cells to a greater degree than it does the tumor cells.

The authors feel that use of this antimetabolite-metabolite pair, in the above manner, may prove to have a place in the therapy of incurable cancer of the head and neck.

Carl J. Pauerstein

Vol. 13, January-February, 1960.

*Graham, R. M., and Graham, J. B.: Sensitization Response in Patients With Cancer of the Uterine Cervix, p. 5.

*Graham, R. M., and Graham, J. B.: Factors in Prognosis of Cancer of the Uterine Cervix—Desquamation of Malignant Cells, p. 15.

*Braunschweig, A.: Surgical Treatment of Stage I Cancer of Cervix, p. 34.

Graham and Graham: Sensitization Response in Patients With Cancer of Cervix, p. 5. The sensitization response (SR) is measured by

The sensitization response (SR) is measured by examination of desquamated nonmalignant parabasal cells of the squamous epithelium of the cervix and vagina as one parameter of host resistence to cancer.

The morphologic criteria for the evaluation of SR are discussed in detail, as are the techniques for obtaining the specimen and preparing the smears. Reproducibility of evaluation of a given smear by the same and different observers is also discussed.

Five series totaling 766 are analyzed. Two of these series are retrospective studies, dealing, respectively, with 147 cases treated by radiation and 129 cases treated by radical hysterectomy and regional lymphodenectomy.

The correlation between SR and 5 year survival in the patients treated radiologically was positive and of a high order of significance. Interestingly, this trend was completely reversed when surgical treatment was used, so that those patients with marked SR had poor 5 year survival, and those with poor SR showed good 5 year survival.

Three prospective series were used to investigate relationship among menopause, age, and sensitization response. While the incidence of SR increases with increasing age and menopause, the prognostic significance of SR is apparently not related to these factors.

Carl J. Pauerstein

Graham and Graham: Factors in Prognosis of Cancer of the Uterine Cervix—Desquamation of Malignant Cells, p. 15.

Study of the rate of desquamation of malignant cells from the surface of a lesion may elucidate the observed variation in metastatic tendency among malignant tumors.

To investigate this possibility 635 patients with primary cancer of the cervix were studied by aspirating material from the posterior vaginal fornix and expressing malignant cells as a percentage of the epithelial cell population. The percentage of malignant cells correlated badly both with clinical staging of the disease and, for lesions greater than 2 cm. in diameter, with the size of the exposed surface of the lesion.

In 192 patients with Stages I and II carcinoma of the cervix treated surgically a good correlation between desquamation of malignant cells and lymph node involvement was noted. Only 8 per cent of patients with less than 1 per cent desquamated malignant cells showed involvement of lymph nodes. In contrast, in the group of patients with 40 per cent desquamated malignant cells lymph node involvement was present in 76 per cent. When patients with Stages I and II cancer of the cervix were treated surgically, progressive decrease in 5 year survival with increasing exfoliated cancer cells was noted. The decreased survival is dispro-

portionate to that accounted for by lymph node involvement alone.

When patients with Stages I and II cancer of the cervix were treated with radiation, the 5 year survival was greatest in those patients shedding the highest percentage of tumor cells A direct correlation between desquamation of tumor cells and sensitization response was also noted.

The incidence of lymph node involvement, percentage of desquamated malignant cells sensitization response in normal basal cells, and 5 year survival are all correlated. They also discuss the possible efficacy of using the percentage of desquamated malignant cells to choose preferentially between surgical or radiation therapy for a given case of carcinoma of the cervix.

Carl J. Pauerstein

Braunschweig: Surgical Treatment of Stage I Cancer of Cervix, p. 34.

Dr. Braunschweig reports on 177 patients with Stage I cancer of cervix treated at Memorial Center from September, 1947, to December, 1953.

These cases were classified clinically as Stage I on initial examination. The extent of the lesion varied from microscopic infiltration to involvement of the entire cervix and/or endocervix.

The author notes that 20 patients were not treated surgically, and enumerates the varied reasons. Four of the patients in whom surgical intervention was undertaken were noted at laparotomy to have disease spread beyond the confines of the pelvis. These cases were excluded from the follow-up study. Of the 153 patients who were operated upon for "cure," an additional 4 patients were excluded. Two were lost to follow-up prior to 5 years, and 2 died of conditions not related to cancer. Of these 153 patients considered, 9 poor-risk patients underwent Schauta type radical vaginal procedures, 10 underwent total hysterectomies, and 2 were subjected to classic Wertheim operations, leaving 132 patients who were treated by radical hysterectomy and pelvic node excision.

The 149 operative patients who were available to 5 year follow-up were subdivided on the basis of size of the lesion, as noted in the pathology reports.

The over-all 5 year survival for these patients was 83 per cent. In 11 patients with posi-

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ive pelvic lymph nodes, the 5 year survival was 0 per cent. In Stage I lesions, ranging in size from 0.5 mm. to involvement of the entire tervix or endocervix, the 5 year salvage, in the absence of pelvic node metastases, was 87 per cent.

The incidence of fistula formation was 10 per cent and the operative mortality was 0.7 per cent.

An additional 18 cases of epidermoid cancer of the cervical stump, treated by excision of the stump and node dissection, are discussed.

Dr. Braunschweig states that methods of prediction of the most beneficial treatment for Stage I cervical cancer, to be significant, must enable salvage rates of better than 87 per cent among patients treated either by radiation or by operation.

Carl J. Pauerstein

Irish Journal of Medical Science

No. 413, May, 1960.

*Feeney, J. K.: Disturbed Ectopic Pregnancy, p. 213.

*Andrews, J. D.: The Use of the Colposcope in Gynecological Diagnosis, p. 237.

Feeney: Disturbed Ectopic Pregnancy, p. 213.

The author reviews 103 personal cases of disturbed ectopic pregnancy seen over a period of 21 years. The cases are divided into categories according to a modification of Monro Kerr's classification, and the significant details are described on this basis.

The practical points which emerge from these wanderings in Ectopia are:

1. In the Dublin Maternities the approximate incidence of ectopic pregnancy which comes to operation is about 1 in 500 pregnancies. The incidence for the country as a whole is about 1 in 1,000. These figures are low compared to those of other countries.

2. The diagnosis must be constantly borne in mind if it is not to be missed. There were no deaths in the cases (103) described here.

3. Many practitioners associate ectopic pregnancy with acute illness characterized by collapse and internal hemorrhage. For this reason they may miss the diagnosis in the so-called ordinary and hematocele varieties.

4. The hematocele variety is frequently misliagnosed because the illness lasts longer and is vague and ill-defined. The change for the better which takes place in the patients' appearance on or about the fifth postoperative day is truly remarkable. 5. The gross disorganization of the pelvic organs noted on abdominal section in the so-called "old missed" variety indicates quite clearly the value of early operation in all cases of ectopic pregnancy.

6. No apology need be made for the performance of abdominal section in doubtful cases of ectopic pregnancy. Even if an ectopic pregnancy is not present, pathological lesions, requiring operative correction, are usually found. Edward Solomons

Andrews: Use of Colposcope in Gynecological Diagnosis, p. 237.

This is a preliminary study from a colposcopy clinic established at St. Bartholomew's Hospital, London. Cases in which the history and cervical appearances were suggestive of cancer and clinically manifest cases of carcinoma of the cervix were specifically excluded from the compilation. Among 285 cases examined there were 2 cases of early carcinoma evident at colposcopy which were clinically unsuspected but confirmed at biopsy. The methods of use, normal appearances, pathological appearances and the clinical applications are fully described.

Edward Solomons

The Journal of the American Medical Association

Vol. 172, March 5, 1960.

*Casady, G. N., Moore, D. C., and Bridenbaugh, L. D.: Postpartum Hypertension After Use of Vasoconstrictor and Oxytocic Drugs, p. 1011.

Casady, Moore, and Bridenbaugh: Postpartum Hypertension After Use of Vasoconstrictor and Oxytocic Drugs, p. 1011.

In a study of 8,000 deliveries performed under continuous caudal block analgesia, the records of 741 patients indicated that the combined effect of a vasoconstrictor and an oxytocic drug, given 3 to 6 hours apart, led to severe hypertension in 34 (4.6 per cent of 741) patients.

The average interval from administration of the vasoconstrictor drugs to the onset of hypertension was 1 hour and 51 minutes. The average interval from administration of the oxytocic drugs to the onset of hypertension was 39½ minutes. A severe, incapacitating headache occurred in about 80 per cent of the cases.

Chlorpromazine (Thorazine) hydrochloride, because of its adrenolytic action, was used to resolve the severe hypertension resulting from the combined use of a vasoconstrictor and an oxytocic drug. The dose given to the patients ranged from 12.5 to 15 mg., and this was given intravenously at a rate of 2.5 mg. every 15 seconds. The indications for treatment with chlorpromazine hydrochloride are sustained elevation of the systolic blood pressure above normal, e.g., an increase of 30 to 40 mm. Hg or a sustained diastolic pressure of 90 mm. Hg or more, or both, with or without a severe, persistent headache.

The authors felt that prophylactic administration of vasoconstrictor drugs should be omitted when regional block anesthesia is used in vaginal delivery. When this was done, the incidence of hypertension dropped from 4.6 to 2 per cent. When a vasoconstrictor drug was used to correct hypotension following caudal block anesthesia, an oxytocic drug was not used.

John J. Dettling

April 2, 1960.

*Vandam, L. D., and Dripps, R. D.: Long-Term Follow-up of Patients Who Received 10,098 Spinal Anesthetics, p. 1483.

Vandam and Dripps: Long-Term Follow-up of Patients Who Received 10,098 Spinal Anesthetics, p. 1483.

A critical evaluation of spinal anesthetics was made by a study of the records of 8,460 patients who received 10,098 injections of spinal anesthetics. A parallel study was conducted in a group of 1,000 persons who were placed under general anesthesia for the same types of operations as those in which the first group were put under spinal anesthesia. A smaller series of 100 patients were placed under spinal anesthesia only after the induction of general anesthesia to assess these symptoms purely on a psychic basis.

No instance of adhesive arachnitis, transverse myelitis, or cauda equina syndrome was found, but neurological complications occasionally resulted from lumbar puncture per se. The common denominator in all of these cases was the multiple insertion of the lumbar-puncture needle with the production of paresthesias in the lumbar and sacral dermatomes.

This paper constitutes a plea for a meticulous technique in the performance of lumbar puncture, not only during spinal anesthesia but also for diagnostic purposes. Possible causes of the development of neurological symptoms after traumatic lumbar puncture include production of a focus of pain in the tissues of the back,

onset of traumatic radiculitis, and development of aseptic hemogenic meningitis.

John J. Dettling

April 16, 1960.

*Moore, G. E., Sandberg, A. A., and Watne, A. L.: Spread of Cancer Cells and Its Relationship to Chemotherapy, p. 1729.

Moore, Sandberg, and Watne: Spread of Cancer Cells and Its Relationship to Chemotherapy, p. 1729.

In a series of 179 patients with advanced cancer, one half of the samples of peripheral blood yielded recognizable tumor cells. Free cancer cells can be identified in the circulating blood by removing the erythrocytes with a heparinfibrinogen mixture, centrifuging the plasma, and examining smears made from the buffy coat.

These metastasizing cells with diameters of 10 to 30 μ could deform and pass through apertures less than 10 μ in diameter and hence could traverse capillary beds. Despite adequate surgical excision of many malignancies, cancer cells undoubtedly remain in the body cavities and may constitute an important source of recurrence.

Tumor cells may also be spread by the physician and surgeon during examination, diagnostic procedures, and operative procedures.

The study of tumor cell dissemination is worthy of attention because of the great number of chemotherapeutic, radioactive, and immunologic agents being found which may have clinical value. Some anticancer agents probably will be useful clinically against unestablished tumor cells, even though they are ineffective systemically against solid tumors.

John J. Dettling

*Sokal, J. E., and Lessmann, E. M.: Effects of Cancer Chemotherapeutic Agents on the Human Fetus, p. 1765.

Sokal and Lessmann: Effects of Cancer Chemotherapeutic Agents on the Human Fetus, p. 1765.

The effects of cancer chemotherapeutic agents on the human fetus have been reviewed. Follow-up information has been assembled on children born to women treated with various cytotox agents during pregnancy; the oldest child traced is now 10 years of age.

The most sensitive period for the induction of malformation in animals appears to be the middle third of pregnancy. The authors have encountered no reports of malformations among

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numan infants exposed to chemotherapeutic agents after the first trimester of intrauterine life. The human fetus is most susceptible to eratogenic agents such as rubella virus and roentgen irradiation during the first trimester, and it is probable that this is also the case for cancer chemotherapeutic drugs.

Aminopterin, in addition to being a potent abortifacient, can induce major fetal abnormalities when administered during the first trimester of pregnancy. Presumably, this would also be true of amethopterin (Methotrexate).

Agents which have been used in pregnancy without inducing fetal abnormalities include nitrogen mustard, urethan, 6-mercaptopurine, and chlorambucil.

Busulfan and 6-mercaptopurine, administered in alternating courses throughout pregnancy, produced multiple severe fetal abnormalities, although neither drug alone produced major fetal damage.

The outcome of all cases of pregnancy in which cancer chemotherapeutic agents have been administered should be reported. The accumulation of detailed information regarding this uncommon clinical problem will serve as a guide to proper management.

John J. Dettling

Vol. 173, May 7, 1960.

*Newman, G., and Nichols, C. R.: Sexual Activities and Attitudes in Older Persons, p. 33.

Newman and Nichols: Sexual Activities and Attitudes in Older Persons, p. 33.

In a comprehensive, interdisciplinary study of geriatric subjects living in Durham, North Carolina, data have been gathered and assessed regarding the sexual activity and attitudes of older people. Subjects ranged from 60 to 93 years of age, with an average of 70 years. A total of 250 were included in this study. One hundred and one subjects were single, divorced, or widowed and about 7 per cent of this group were sexually active. The remaining 149 subjects were still married and living with their spouses, and of these, 54 per cent indicated that they were still exually active to some degree.

The Negro subjects were sexually more active than the Caucasian; men more active than women, and persons of lower socioeconomic status more active than those of higher socioeconomic status.

The subjects also rated themselves on the rela-

tive strength of their sexual urge in youth and in old age, and a comparison of the two ratings shows a remarkable constancy of the experiencing of the sexual drive within individual persons throughout life.

Sexual interest and activity decline with advancing years, but cessation of sexual activity in the oldest subjects was often found to be related to decline in physical health of one or both of the marital partners.

John J. Dettling

July 2, 1960.

*Fish, S. A.: Maternal Death Due to Disseminated Varicella, p. 978.

Fish: Maternal Death Due to Disseminated Varicella, p. 978.

Four fatal cases of chickenpox occurring during pregnancy are reported. Each patient died of the characteristic diffuse interstitial pneumonitis. In none of these 4 cases did the infant survive. There is apparently no specific tendency or increased susceptibility to chickenpox during pregnancy.

The salient clinical features of disseminated varicella are as follows:

- 1. The patient is almost always an adult who has been vaccinated for smallpox but who never had chickenpox.
- 2. The typical vesiculopapular polymorphus rash of chickenpox appears approximately 14 to 16 days after exposure.
- 3. Evidence of systemic involvement appears on the second or third day after eruption of the rash. Respiratory symptoms are the first and most serious to occur. There is rapid progression from a persistent cough to hemoptysis, dyspnea, tachypnea, and cyanosis.
- 4. Physical examination of the lungs may result in normal findings or scattered râles, with occasional rhonchi and wheezes.
- 5. Laboratory studies disclose a normal or slightly elevated white blood cell count, with no significant left shift. Sputum and blood cultures are negative as are all agglutination studies.
- 6. Roentgenographic examination of the chest shows a characteristic diffuse, fine nodular infiltration throughout both lung fields without evidence of consolidation.
- 7. The mortality among patients with disseminated chickenpox has been estimated to be between 10 and 30 per cent.

Treatment is directed toward maintaining adequate pulmonary exchange and water balance

until the disease resolves spontaneously. There is no antibiotic that is specific for this disease.

It has been advised that routine chest x-ray examination be performed on all adult patients with chickenpox.

John J. Dettling

The Journal of Clinical Endocrinology and Metabolism

Vol. 20, June, 1960.

*Hobkirk, R., Blahey, P. R., Alfheim, A., Raeside, J. I., and Joron, G. E.: Urinary Estrogen Excretion in Normal and Diabetic Pregnancy, p. 805.

*Schon, M., and Sutherland, A. M.: The Role of Hormones in Human Behavior. III. Changes in Female Sexuality After Hypophysectomy, p. 833.

Hobkirk et al.: Urinary Estrogen Excretion in Normal and Diabetic Pregnancy, p. 805.

Urinary levels of estriol, estrone, and estradiol- 17β increase during the last 20 weeks of pregnancy in a qualitatively similar fashion in both the normal and diabetic states. The relative amounts of these estrogens found in the urine suggest that they arise from the same source in both groups according to the transformation, estradiol

estrone → estriol. It also appears likely that there is an additional source of estriol in the two groups, particularly in late pregnancy. There is a tendency for estriol levels to be lower in diabetic than in nondiabetic pregnancy. Considerable variability in the relative amounts of these three estrogens from one pregnancy to another, both diabetic and normal, suggests the occurrence of a varying pattern of estrogen metabolism from one individual to another.

I. Edward Hall

Schon and Sutherland: Role of Hormones in Human Behavior. III, p. 833.

A study was made of the sexual functioning of women with metastatic breast cancer who had undergone hypophysectomy as a therapeutic measure to check the progress of the disease. The study was divided into two phases. In the first phase, 20 women, mean age 51 years, were interviewed before and after hypophysectomy with regard to their sexual functioning. In the second phase, 30 women, mean age 51 years, were studied after hypophysectomy. Emphasis was placed on three aspects of sexual behavior, i.e., desire, activity, and gratification. Of the 30 women in the second phase, 23 had previously

undergone mastectomy and 7 oophorectomy; the sexual reactions to all three types of operation were investigated. Results indicated that neither mastectomy nor oophorectomy had a significant influence on the sexual functioning of these women whereas hypophysectomy resulted in a sharp decrease of sexual desire, activity, and gratification. It was concluded that absence of the tropic pituitary hormone which activates the adrenal androgens (seemingly the only source of androgen in women) accounted for the decline in sexual functioning. This conclusion was based on the following: (1) the postoperative administration of thyroid hormones or of cortisone had no effect on the sexual status after operation; (2) results of studies reported in the literature indicate that deprivation of ovarian hormones does not appreciably affect sexual behavior. Thus, lack of adrenal androgens appears to be the chief cause of the sharp drop in female sexual activity after hypophysectomy.

J. Edward Hall

July, 1960.

*Currie, A. R., Adamsons, H., and van Dyke, H. B.: Vasopressin and Oxytocin in the Posterior Lobe of the Pituitary, p. 947.

*Swanson, H. E., and Ezrin, C.: The Natural History of the Delta Cell of the Adenohypophysis: In Childhood, Adulthood and Pregnancy, p. 952.

Currie, Adamsons, and van Dyke: Vasopressin and Oxytocin in the Posterior Lobe of the Pituitary, p. 947.

The posterior pituitary lobes from 9 patients, 6 female and 3 male, who died from a variety of illnesses were assayed individually for vasopressin (vasopressor and antidiuretic responses) and oxytocin (milk-ejection activity). There was a remarkable variation in the vasopressin-oxytocin ratio, and this suggests that the hormones are not present in a fixed proportion bound to a protein in the glands in man. Age, sex, stress as assessed by the lipid pattern in the adrenal cortex, the disease state, and steroid therapy had no obvious influence on the yield of vasopressin and oxytocin in the small series of cases studied.

J. Edward Hall

Swanson and Ezrin: Natural History of Delta Cell of Adenohypophysis, p. 952.

With use of the iron-PAS stain, counts were made of the cells in the pituitaries of 69 chil-

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dren and 44 pregnant or postpartum women. The results were analyzed statistically. No delta cells were found before the age of 10, after which the percentage of delta cells gradually increased. Also no delta cells were found after the first trimester of pregnancy. These observations suggest that delta cells produce and store gonadotrophin. A further analysis of data obtained on a group of 71 nonendocrine adult patients showed a greater percentage of delta cells in men past the age of 60 than in women of corresponding age. On the other hand, the pituitaries of these women contained a higher percentage of gamma cells. These gamma cells probably also secrete gonadotrophin but store little of the hormone.

J. Edward Hall

The Lancet

Vol. 1, Feb. 27, 1960.

*Wilkinson, M.: The Carpal-Tunnel Syndrome in Pregnancy, p. 253.

*Macafee, C. H. G.: Placenta Praevia, p. 449. Wilkinson: Carpal-Tunnel Syndrome in Pregnancy, p. 253.

Fourteen instances of acroparesthesia are discussed. All the patients complained of numbness, tingling, or pain in the fingers of one or both hands. The thumb, index, and middle fingers were most often involved. When both hands were involved the symptoms appeared first in the dominant hand in 3 and in both hands simultaneously in 2 instances. In the remaining 9 patients the symptoms appeared in the dominant hand only. Seven patients had a feeling of tenseness or objective swelling of the hands. One of the latter patients had to have her wedding ring cut off. None of these patients had evidence of toxemia, and backache occurred in only 4 of these patients. Eleven of the patients had diminished awareness of pinprick or cotton wool in the distribution of the median nerve. Three had wasting and weakness of the thenar nuscles. Reflex changes were found in 5 paients (diminished triceps jerk, 4; diminished bieps jerk, 1). Pain in the neck was experienced by 2 patients and pain in the wrist and forearm by 5. The cervical spine was x-rayed in 12 patients (slight loss of normal curve, 8; diminution of one or more disc spaces, 4; narrowing of intervertebral foramina, 2). No x-rays of the wrists were obtained.

One patient required-decompression of the median nerve 10 months after delivery and one

patient had persistent symptoms for 9 months, at which time cervical spondylosis was demonstrated by x-ray. Other than in these 2 patients symptoms did not persist long (average 10.1 weeks). Other than sedation no specific therapy was usually required.

Concerning etiology, the author speculates about the possible relation of (1) trauma including the performance of unwanted household jobs, (2) weight increase, particularly as in this series—5 patients gained 30 pounds or more including one patient who gained 60 pounds, (3) relaxin, since all ligaments tend to relax during pregnancy those of the carpal tunnel may be involved affecting the results of stress and strain at the wrist, (4) posture. Four patients found it more comfortable to sleep on their backs and 5 found the pain worse when they slept on the affected side. The suggestion is made that redistribution of fluid may play a part in etiology.

David M. Kydd

Macafee: Placenta Praevia, p. 449.

In this report of a lecture given at Queen Charlotte's Hospital, London, the author states some of his beliefs concerning placenta previa. Over the course of approximately 100 years the maternal mortality fell from 30 to 5 per cent in 1939 but during the same period the fetal mortality changed only a little, from 60 to 54 per cent. Since 1939 the introduction of modern treatment has been accompanied by a drop in fetal mortality to about 10 per cent and, under the best of circumstances, by an absence of maternal mortality. The author ascribes this improvement to the now general practice of rapidly transferring pregnant patients who have vaginal bleeding of any cause to well-equipped hospitals without prior vaginal examination and to the adoption of expectant treatment. If the pregnancy has reached 37 to 40 weeks delay in treatment is unwarranted. After the patient is prepared for possible transfusion of blood an attempt should be made to diagnose the cause of the hemorrhage. Often abdominal examination will go a long way in making the diagnosis of placenta previa and of its site. The final answer can be given only by vaginal examination but this must be done only with the patient on the operation table and only when preparations for meeting emergencies have been completed.

If the first episode of bleeding occurs at 30 to 34 weeks or before, expectant treatment is im-

portant. Catastrophic spontaneous hemorrhage is rare, but persistent or repeated small hemorrhages may result in serious anemia. Consequently, during the period of waiting any maternal anemia that is discovered should be treated if necessary by transfusion of blood. The author reports 3 series of patients who received expectant treatment in which the maternal mortality was 1 per cent or less (none in the author's series) and the fetal mortality was 20.8, 14.7, and 8.5 per cent in the 3 series, the last being the author's own series. As an aid in the differential diagnosis of the causes of antepartum hemorrhage (placenta previa, separation of a normally situated placenta, hemorrhage from circumvallate placenta, toxic accidental hemorrhage in a patient with a placenta previa, cervical polyp, carcinoma of the cervix), roentgenography is of limited value.

Cesarean section is desirable in most instances of placenta previa and now between 60 and 70 per cent are delivered by this method usually but not inevitably by lower segment cesarean section. The situation of the umbilical cord in relation to the internal os is of vital importance because the cord is often placed excentrically and if the insertion is just inside the internal os cesarean section may be the only means of delivering a live child. While cesarean section has improved results for both mother and child uncontrollable hemorrhage or extensive placenta

accreta may require quick decisions and perhaps radical operation.

Although cesarean section is required in the majority of instances of placenta previa, lesser degrees may be treated by rupture of the membranes. If the placenta is lying posteriorly, however, and pressing the fetal head into the pelvis results in disturbing the fetal heart, an excentric position of the umbilical cord must be suspected. In such instances rupture of the membranes may result in prolapse or compression of the cord causing fetal death. Except where the baby is very immature or already dead, bipolar version has been almost abandoned.

The author states that the beneficial results from expectant treatment he reports have been criticized. In India Quereshi has reported an increase in the use of cesarean section. This has resulted in a decreased maternal mortality (from 21.9 to 5.8 per cent) but no appreciable change in perinatal mortality (from 71.3 to 60.2 per cent). In Africa also the expectant method of treatment has been criticized. The author states that there is some validity in these criticisms in that the success is dependent upon rapid transport of the patient to a well-equipped hospital before any vaginal examination or other treatment is attempted. Also patients who have had cesarean sections must receive expert obstetrical care during subsequent pregnancies and this is not always possible in less highly developed so-David M. Kydd

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James W. Kennedy Memorial Travel Fellowship

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The American Association of Obstetricians and Gynecologists announces the establishment of a Travel Fellowship in memory of the late Dr. James W. Kennedy.

This Fellowship will provide \$6000 for a young man or woman to pursue a year of graduate study in a foreign country in obstetrics and gynecology, or in an allied field, which will help him become an outstanding clinician and teacher.

The first Travel Fellowship will start July 1, 1961, and extend for one year. A minimum of 3 years of residency training in obstetrics and gynecology is a prerequisite. Candidates are also eligible who have completed their residency training and are full-time members of a department of obstetrics and gynecology of a medical school in the United States or Canada.

Candidates interested in the Travel Fellowship should write to Dr. F. Bayard Carter, Chairman of the Committee, Department of Obstetrics and Gynecology, Duke University Medical Center, Box 3705, Duke Station, Durham, North Carolina, for application blanks. Other members of the Committee are Dr. Ernest W. Page, University of California School of Medicine, San Francisco 22, California, and Dr. E. Stewart Taylor, University of Colorado School of Medicine, Denver 20, Colorado. Selection of the candidate will be made on or about April 1, 1961, and applications must be in the hands of the Chairman not later than March 1, 1961.

American Board of Obstetrics and Gynecology

The Part I examinations (written) will be held in various cities of the United States, Canada, and military centers outside the Continental United States on Friday, Jan. 13, 1961.

Reopened candidates will be required to submit case reports for review thirty days after notification of eligibility.

Scheduled Part I candidates are also required to submit their 20 case abstracts in order to complete the Part I examination.

Current Bulletins outlining present requirements may be obtained by writing to the executive secretary's office.

Robert L. Faulkner, M.D. Executive Secretary and Treasurer 2105 Adelbert Road Cleveland 6, Ohio

International Fertility Association

The sectional meeting on fertility and sterility of North, Central, and South America, sponsored by the International Fertility Association, will be held at the Hotel El Presidente, Acapulco, Mexico, Jan. 28-31, 1961.

For further information write Maxwell Roland, M.D., Treasurer, International Fertility Association, 109-23 71st Road, Forest Hills, New York.

Erratum. The title of the article by Gray H. Twombly and Mortimer Levitz on page 889 of the November Journal should have read, "Metabolism of estrone-16-C14 sulfate in women."

Roster of American obstetrical and gynecological societies*

(Appears in January and July)

American College of Obstetricians and Gynecologists. (1951) President, C. Paul Hodgkinson. Secretary, Craig W. Muckle, 1806 Garrett Rd., Lansdowne, Pa. Next meeting, April 21-28, 1961, Americana, Bal Harbour, Fla.

American Gynecological Society. (1876) President,
 Albert H. Aldridge. Secretary,
 Andrew A. Marchetti,
 Georgetown University Hospital,
 Washington 7,
 D. C. Next meeting,
 The Broadmoor,
 Colorado Springs,
 Colo.,
 May 29-31,
 1961.

American Association of Obstetricians and Gynecologists. (1888) President, John L. Parks.
 Secretary, Clyde L. Randall, 100 Meadow Rd., Buffalo 16, N. Y. Meetings, March 11-12, 1961, Sept. 7-9, 1961, The Homestead, Hot Springs, Va.

Central Association of Obstetricians and Gynecologists. (1929) President, Edwin J. DeCosta. Secretary, Herman L. Gardner, 6436 Fannin, Houston 25, Texas. Annual meeting, The Statler-Hilton, Cleveland, Oct. 5-7, 1961.

Akron Obstetrical and Gynecological Society. (1946) President, Robert M. DeWitt. Secretary, Richard J. Yoder, 180 First St., N.W., Barberton, Ohio. Meetings, third Friday, January, April, June, and October.

Alabama Association of Obstetricians and Gynecologists. (1940) President, James French. Secretary, Joe Garner, Medical Center, Dothan, Ala. Meetings, spring and fall.

Alameda County Gynecological Society. (1951)

South Atlantic Association of Obstetricians and Gynecologists. (1938) President, John B. Cross. Secretary, Lawrence L. Hester, Jr., 55 Doughty St., Charleston, S. C. Next meeting, Feb. 15-18, 1961, Biltmore Hotel, Atlanta, Ga

A. M. A. Section on Obstetrics and Gynecology. (1859) Chairman, Curtis J. Lund, Rochester, N. Y. Secretary, Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, June 26-30, 1961, New York, N. Y.

Society of Obstetricians and Gynaecologists of Canada. (1944) President, Elinor F. E. Black. Secretary, F. P. McInnis, 280 Bloor St., W., Toronto 5. Annual meeting, The Chantecler, Ste. Adele en haut, Que., June 16-18, 1961.

American Board of Obstetrics and Gynecology, Inc. (1930) President, F. Bayard Carter. Executive secretary, Robert L. Faulkner, 2105 Adelbert Rd., Cleveland 6. Next meeting, April 8-15, 1961.

President, Clifford C. Chappell, Jr. Secretary, Donald H. Minkler, 2915 Telegraph Ave., Berkeley, Calif. Meetings, fourth Wednesday, September through May except December.

Arkansas Obstetrical and Gynecological Society. (1953) President, J. B. Kittrell. Secretary, J. W. Harrison, 401 5th St., Texarkana, Texas Meetings, spring and fall.

Atlanta Obstetrical and Gynecological Society. (1954) President, George A. Holloway. Secretary, William M. Lester, 272 Boulevard N.E., Atlanta 12, Ga. Meetings, October February, April, and June.

Birmingham Obstetrical and Gynecological Society. (1949) President, Wade Cline. Secretary, George C. Douglas, 1920 15th Ave., S., Birmingham 5, Ala. Meetings, third Thursday, September, November, January, and April.

^{*}Changes, omissions, and corrections must be received by the publisher two months in advance, by May 1 for the July Roster and by November 1 for the January Roster. Please address The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Missouri. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

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- Boston, Obstetrical Society of. (1861) President, John L. Newell. Secretary, Luke Gillespie, 221 Longwood Ave., Boston 15, Mass. Meetings, third Monday, January, February, March, April, October, and November.
- Bronx Gynecological and Obstetrical Society. (1924) President, A. Charles Posner. Secretary, William J. Farrell, 2960 Grand Concourse, Bronx, N. Y. Meetings, fourth Monday, October through May.
- Brooklyn Gynecological Society, Inc. (1890)

 President, J. Thornton Wallace. Secretary,
 Robert E. Gordon, 32 Remsen St., Brooklyn
 1, N. Y. Meetings, third Wednesday, January,
 February, March, April, May, October, and
 November.
- Buffalo Obstetrical and Gynecological Society. (1946) President, Chester J. Kaminski. Secretary, Milford Childs, 2900 Main St., Buffalo 14, N. Y. Meetings, first Tuesday, September through May.
- Central New York Association of Gynecologists and Obstetricians. (1938) President, Wendell George. Secretary, James N. Capps, 325 University Ave., Syracuse 10, N. Y. Meetings, third Tuesday, September, November, January, March, and May.
- Chicago Gynecological Society. (1878) President,
 Edwin J. DeCosta. Secretary, Charles P.
 McCartney, 5841 Maryland Ave., Chicago 37.
 Meetings, third Friday, October through June.
- Cincinnati Obstetrical and Gynecological Society.

 (1876) President, Richard T. F. Schmidt.

 Secretary, Arthur G. King, 199 William

 Howard Taft Rd., Cincinnati 19, Ohio. Meetings, third Thursday, September through

 June.
- Cleveland Society of Obstetrics and Gynecology. (1947) President, Marion E. Black. Secretary, Richard Glove, 3550 Warrensville Center Rd., Shaker Heights 22, Ohio. Meetings, fourth Monday, September, November, January, March, and May.
- Columbus Obstetrical and Gynecological Society.
 (1944) President, Ben E. Jacoby. Secretary,
 Francis W. Gallagher, 375 E. Town St., Columbus, Ohio. Meetings, fourth Wednesday of month, September through June, except December.
- Connecticut Society of American Board Obstetricians and Gynecologists, Inc. (1952) President, Joseph Klein. Secretary, Robert H. Wyatt, 1 Perryridge Rd., Greenwich, Conn. Annual meeting, first Thursday in October. Semiannual meeting in conjunction with

- spring meeting of the Connecticut State Medical Society.
- Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) President, Wayne T. Robinson. Secretary, James T. Downs, III, 3707 Gaston Ave., Dallas 10, Texas. Meetings, spring and fall.
- Dayton Obstetrical and Gynecological Society. (1937) President, Nicholas J. Thompson. Secretary, W. S. Dietrichson, 252 Talbott Bldg., Dayton 2, Ohio. Meetings, third Wednesday each month, September through April.
- Denver Gynecological and Obstetrical Society. (1942) President, Raymond C. Chatfield. Secretary, George M. Horner, 3705 E. Colfax Ave., Denver 6, Colo. Meetings, first Monday October through May.
- Florida Obstetric and Gynecologic Society. (1948) President, T. Bert Fletcher. Secretary, Sam W. Denham, 1661 Riverside Ave., Suite A., Jacksonville 4, Fla. Next meeting, May 27, 28, 1961.
- Georgia State Obstetrical and Gynecological Society. (1951) President, William K. Jordan. Secretary, C. I. Bryans, Jr., 1139 Druid Park Ave., Augusta, Ga., Meetings, spring and fall.
- Harris, John Warton, Obstetrical Society. (1953)

 President, William V. Luetke. Joint Secretaries,
 Madeline Thornton and William Keikhofer,
 University Hospitals, 1300 University Ave.,
 Madison, Wis. Annual meeting in May.
- Honolulu Obstetrical and Gynecological Society. (1947) President, Sydney Fujita. Secretary, Arno J. Mundt, Room 405, Diccingham Bldg., Honolulu 13, Hawaii. Meetings, third Monday of each month.
- Houston Gynecological and Obstetrical Society. (1956) President, Seward H. Wills. Secretary, Mary Ann McKinney, 5000 Montrose Blvd., Houston 6, Texas. Meetings, quarterly.
- Idaho Obstetrical and Gynecological Society.

 President, Ralph Hegsted. Secretary-treasurer,
 E. S. Bills, 798 S Boulevard, Idaho Falls,
 Idaho.
- Illinois Obstetrical and Gynecological Society. (1946) President, David M. Jenkins. Secretary, Deane M. Farley, 6804 Windsor Ave., Berwyn, Illinois. Meetings, September, January, and May.
- Indiana Obstetrical and Gynecological Society.
 (1947) President, David Bickel. Secretary,
 Floyd T. Romberger, Jr., 3440 N. Meridian
 St., Indianapolis 8, Ind. Meetings, January,
 May, and October.

- Interurban Obstetrical and Gynecological Society. (1949) President, Raymond J. Pieri. Secretary, E. R. Duggan, 1351 Mt. Hope Ave., Rochester 20, N. Y. Meeting, October, 1961.
- Iowa Obstetrical and Gynecological Society. (1947) President, Richard Bausch. Secretary, Clifford P. Goplerud, State University of Iowa Hospitals, Iowa City, Iowa. Meetings, fall and winter.
- Jacksonville Obstetrical and Gynecological Society. (1960) President, John J. Fisher. Secretary, Doris N. Carson, 836 Miami Rd., Jacksonville, Fla. Meetings, April, August, and December.
- Kansas City Gynecological Society. (1922) President, Kenneth S. Nicolay. Secretary, Joseph C. Williams, 425 East 63rd St., Kansas City, Mo. Meetings, September, November, January, March, and May.
- Kentucky Obstetrical and Gynecological Society. (1947) President, John H. Siehl. Secretary, Edward G. Honey, 300 East Third St., Newport, Ky. Annual meeting, May 18-20, 1961, Cincinnati, Ohio.
- Long Beach Obstetrical and Gynecological Society. (1954) President, Keith C. White. Secretary, A. F. Forster, 3019 Bellflower, Long Beach, Calif. Meetings, third Tuesday, August, October, December, February, March, and May.
- Los Angeles Obstetrical and Gynecological Society, Inc. (1914) President, John L. Gaspar. Secretary, Keith P. Russell, 5478 Wilshire Blvd., Room 222, Los Angeles 36, Calif. Meetings, second Tuesday, September, November, January, March, and May.
- Louisville Obstetrical and Gynecological Society. (1923) President, William C. Durham. Secretary, Harold W. Baker, Heyburn Bldg., Louisville 2, Ky. Meetings, fourth Monday, September through May.
- Madison Obstetrical and Gynecological Society. (1950) President and Secretary, John Healy, Gorham St., Madison, Wis. Meetings, first Tuesday each month.
- Maryland Obstetrical and Gynecological Society.
 (1929) President, Bernard Brack. Secretary,
 D. Frank Kaltreider, University Hospital,
 Lockwood and Greene Sts., Baltimore 1, Md.
 Meetings, Jan. 5, March 2, and May 4, 1961.
- Memphis Obstetrical and Gynecological Society.
 (1950) President, Glenn H. Williams. Secretary, Charles R. Riggs, 166 N. Bellevue, Memphis, Tenn. Meetings, second Tuesday, October through May.

- Miami Obstetrical and Gynecological Society. (1946) President, J. Robert Sory. Secretary, Norman McLeod, 249 Sevilla Ave., Coral Gables, Fla. Meetings, second Thursday, January, March, May, and November.
- Michigan Society of Obstetricians and Gynecologists. (1924) President, James H. Beaton. Secretary, Robert G. Swanson, 314 Eastland Center Professional Bldg., Detroit 36, Mich. Meetings, Feb. 7, April 6, and May 3, 1961.
- Milwaukee Gynecological Society. (1951) President, John W. R. Thoma. Secretary-treasurer, Lester H. Verch, 421 E. Wisconsin Ave., Milwaukee 2, Wis. Meetings, last Monday, November, January, March, and April.
- Minneapolis Obstetrical and Gynecological Society. (1955) President, Charles H. McKenzie. Secretary, Richard R. Fliehr, 301 Doctors Bldg., Minneapolis 2. Meetings, four times a year.
- Minnesota Obstetrical and Gynecological Society. (1936) President, Charles H. McKenzie. Secretary, Alex Barno, 4959 Excelsior Blvd., Minneapolis 16, Minn. Meetings, April and November.
- Missisippi Obstetrical and Gynecological Society. (1947) President, Michael Newton. Secretary, John T. Kitchings, 514B East Woodrow Wilson, Jackson, Miss. Meetings, May and June.
- Mobile County Obstetrical and Gynecological Society. (1949) President, N. L. Brown. Secretary, John F. Vanhoof, 1367 Government St., Mobile, Ala. Meetings, second Wednesday every third month.
- Montana State Obstetrical and Gynecological Society. (1946) President, Richard H. Leeds. Secretary, Joseph H. Brancamp, Mayer Bldg., 10 S. Idaho, Butte, Mont. Next meeting, May 6, 1961, Great Falls, Mont.
- Nashville Obstetrical and Gynecological Society. (1955) President, Edwin L. Williams. Secretary, B. K. Hibbett, III, 2122 West End Ave., Nashville 5, Tenn. Meetings, second Tuesday in January, April, July, and October.
- Nassau Obstetrical and Gynecological Society. (1944) President, Francis D. Maloney. Secretary, William H. Murphy, 15 Clinton Ave. Rockville Center, N. Y. Meetings, third Monday, September, November, February, and May.
- New England Obstetrical and Gynecological Society. (1929) President, Clyde Swett. Secretary, William A. Lynch, 1101 Beacon St., Brookline 46, Mass. Next meeting, May, 1961.

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New Haven Obstetrical Society. (1946) President, Irving Friedman. Secretary, Edward Day, 610 Campbell Ave., West Haven, Conn. Meetings, third Tuesday, September, November, January, March, and May.

New Jersey Obstetrical and Gynecological Society. (1947) President, Harold Schwartz.

Secretary, Christopher T. Reilly, 530 N.

Maple Ave., Ridgewood, N. J. Meetings,

April and October.

New Mexico Obstetrical and Gynecological Society. (1947) President, Henry R. Hyslop. Secretary, William C. Johns, 717 Encino Place, N.E., Albuquerque, N. Mex. Meetings, quarterly.

New Orleans Gynecological and Obstetrical Society. (1924) President, Daniel W. Beacham. Secretary, Frank Nix, 1430 Tulane Ave., New Orleans 12, La. Meetings, October, November, January, March; annual meeting, May, 1961.

New York Obstetrical Society. (1863) President,
Carl T. Javert. Secretary, Saul B. Gusberg,
180 Fort Washington Ave., New York 32,
N. Y. Meetings, second Tuesday, September through May.

North Carolina Obstetrical and Gynecological Society. (1932) President, James A. Crawell. Secretary, Kenneth A. Podger, Durham Surgi-

cal Clinic, Durham, N. C.

North Dakota Society of Obstetrics and Gynecology. (1938) President, John S. Gillam. Secretary, G. Wilson Hunter, Fargo Clinic, Fargo, N. D. Meetings, May 8, 1961; Sept. 15, 16, 1961.

Northeastern New York Obstetrical and Gynecological Society. (1935) President, John Latcher. Secretary, David Tomilson, 2144 Burdett Ave., Troy, N. Y. Meetings, fourth Thursday, January, April, and September.

Northern California Obstetrical and Gynecological Society. (1955) President, Warren E. Jones. Secretary, Andrew M. Henderson, Jr., 2901 Capitol Ave., Sacramento, Calif. Meet-

ings, quarterly.

Oklahoma City Obstetrical and Gynecological Society. (1940) President, Milton Serwer. Secretary, Sam Hendrix, 301 N.W. 12th St., Oklahoma City, Okla. Meetings, third Wednesday each month.

Omaha Obstetrical and Gynecological Society. (1947) President, Walter J. Holden. Secretary, William Boelter, 525 Doctors Bldg., Omaha, Neb. Meetings, third Wednesday, January, March, May, September, and November. Oregon Society of Obstetricians and Gynecologists. (1946) President, John Kirk. Secretary, Richard Franklin, 6815 S.W. 11th Dr., Portland 19, O're. Meetings, third Friday, October through May, except December.

Pacific Coast Obstetrical and Gynecological Society. (1931) President, Donald W. deCarle.
Secretary, Keith Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Meeting, Sept. 20-23, 1961, Yosemite National Park, Calif.

Pacific Northwest Obstetrical and Gynecological Association. (1947) President, Duncan R. Neilson. Secretary, Clifford L. Fearl, 1133 S.W. Market St., Portland 1, Ore. Next meeting, Gearhart, Ore., June 18-20, 1961.

Philadelphia, Obstetrical Society of. (1868)
President, J. Edward Lynch. Secretary, George
C. Lewis, Jr., 133 S. 36th St., Philadelphia 4,
Pa. Meetings, first Thursday, October through

May.

Phoenix Obstetrical and Gynecological Society. (1959) President, Clarence Warrenburg. Secretary, William D. Lawrence, 1313 N. Second St., Phoenix, Ariz. Meetings, January, March, May, September, and November.

Pittsburgh Obstetrical and Gynecological Society. (1934) President, Joseph Loughrey. Secretary, Dean Shannon, Medical Arts Bldg., Butler,

Pa.

Portland Society of Obstetricians and Gynecologists. (1928) President, Ronald P. Neilson. Secretary, W. O. Thomas, Jr., 1735 N. Wheeler Ave., Portland, Ore. Meetings, fourth Wednesday, September through May.

Queens Gynecological Society. (1948) President, Max Friedman. Secretary, B. Edmond Thomas, 30 Grace Ave., Great Neck, N. Y. Meetings, second Wednesday, October, December, Feb-

ruary, and April.

Rochester Obstetrical and Gynecological Society. (1939) President, William Lange. Secretary, George C. Trombetta, 39 N. Goodman St., Rochester 7, N. Y.

St. Louis Gynecological Society. (1924) President, Roy V. Boedeker. Secretary, Bryce H. Bondurant, 950 Francis Place, St. Louis 5, Mo. Meetings, Feb. 9, April 13, 1961.

San Antonio Obstetrical and Gynecological Society. President, G. G. Passmore. Secretary, Frank M. Posey, Jr., 101 N. McCollough, San

Antonio, Texas.

San Diego Gynecological Society. (1937) President, James R. Phalen. Secretary, Francis L. Rook, 3650 Clairemont Dr., San Diego 17, Calif. Meetings, monthly.

- San Francisco Gynecological Society. (1929)
 President, Edmund Overstreet. Secretary,
 Carl Goetsch, 2915 Telegraph Ave., Berkeley
 5, Calif.
- Seattle Gynecological Society. (1941) President, Walter S. Keifer, Jr. Secretary, Donald M. McIntyre, 1120 Cherry, Seattle, Wash. Meetings, third Wednesday, September, October, November, January, March, and April.
- South Carolina Obstetrical and Gynecological Society. (1946) President, Rowland F. Zeigler. Secretary, J. Richard Sosnowski, 231 Calhoun St., Charleston, S. C. Next meeting, October, 1961.
- South Dakota Society of Obstetrics and Gynecology. (1952) President, Charles A. Stern. Secretary, H. H. Theissen, 728 Columbus St., Rapid City, S. D. Meetings, May and October.
- Southeastern Obstetrical and Gynecological Society. President, John R. McCain. Secretary,
 T. Bert Fletcher, Jr., P.O. Box 3488, MSS,
 1203 Miccosukee Rd., Tallahassee, Fla. Meeting, spring.
- Southern California, Obstetrical and Gynecological Assembly of. (1945) President, Keith P. Russell. Secretary, Leon K. Shulman, 435 N. Rosbury Dr., Beverly Hills, Calif. Next meeting, Los Angeles, Feb. 13-17, 1961.
- Southwest Obstetrical and Gynecological Society. (1951) President, John Wanless. Secretary, Charles Franklin, 7808 El Cajon Blvd., La Mesa, Calif. Next meeting, Oct. 15-17, 1961, San Diego.
- Tennessee State Obstetrical and Gynecological Society. President, Harold Schwartz. Secretary, George A. Mitchell, 521 Doctor's Bldg., Chattanooga 3. Meetings, yearly in April.
- Texas Association of Obstetricians and Gynecologists. (1930) President, Oran Prejean. Secretary, Hugh W. Savage, 815 Fifth Ave., Ft. Worth, Texas. Annual meeting, Feb. 18, 1961, Houston.

- Tucson Obstetrical and Gynecological Society. (1954) President, L. D. Sprague. Secretary, Donald Bethune, 620 N. Country Club, Tucson, Ariz. Meetings, second Monday, September, November, January, March, and May.
- Tulsa Obstetrical and Gynecological Society. (1955) President, William F. Thomas, Jr. Secretary, John W. Ward, 2021 S. Lewis Ave., Tulsa 4, Okla. Meetings, second Wednesday, September, November, January, and May.
- Utah Obstetrical and Gynecological Society. (1948) President, Thomas M. Feeny. Secretary, E. Conrad Monson, 2955 Harrison Blvd., Ogden, Utah. Meetings, October, December, February, and May.
- Virginia Obstetrical and Gynecological Society. (1936) President, P. Harrison Picot. Secretary, Brock D. Jones, Jr., 1204 Colonial Ave., Norfolk 17, Va. Meetings, spring and fall.
- Washington Gynecological Society. (1933) President, George Ellis. Secretary, Jed W. Pearson, Jr., 1834 K St., N.W., Washington, D. C. Meetings, January, March, and May.
- Washington State Obstetrical Association. (1936)
 President, Fredric Balz. Secretary, Carter A.
 Swanson; Executive secretary, Dorothy Jones,
 1120 Cherry St., Seattle 4, Wash. Next meeting, May 6, 1961.
- West Texas Obstetrical and Gynecological Society. (1954) President, R. Lee Rode. Secretary, H. Ray Buzbee, 1101 N. 19th St., Abilene, Texas. Meeting, November, 1961.
- Westchester Obstetrical and Gynecological Society. (1939) President, Joshua M. Davies. Secretary, James M. Greer, 170 Maple Ave., White Plains, N. Y. Meetings, second Wednesday, October, November, January, February, March, and May.
- Wisconsin Society of Obstetrics and Gynecology. (1940) President, David Werner. Secretary, John J. Boersma, 306 Cherry St., Green Bay, Wis. Meetings, spring and fall.



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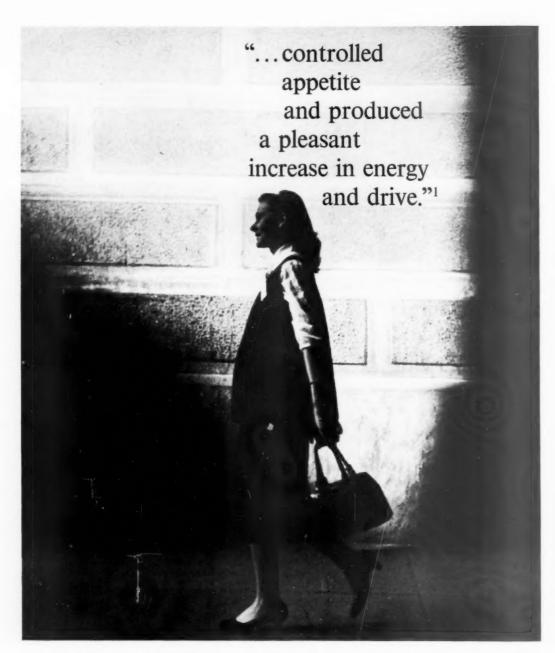
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- 1. Karnaky, K.J., Tri-State Med. Journal, June, 1960
- 2. Schaefer, George, Clin. Obst. & Gynec., June, 1959
- 3. Burrus, Swan, Jr., Am. J. Obst. & Gynec., Aug., 1960
- 4. Liswood, R., Obst. & Gynec., May, 1959

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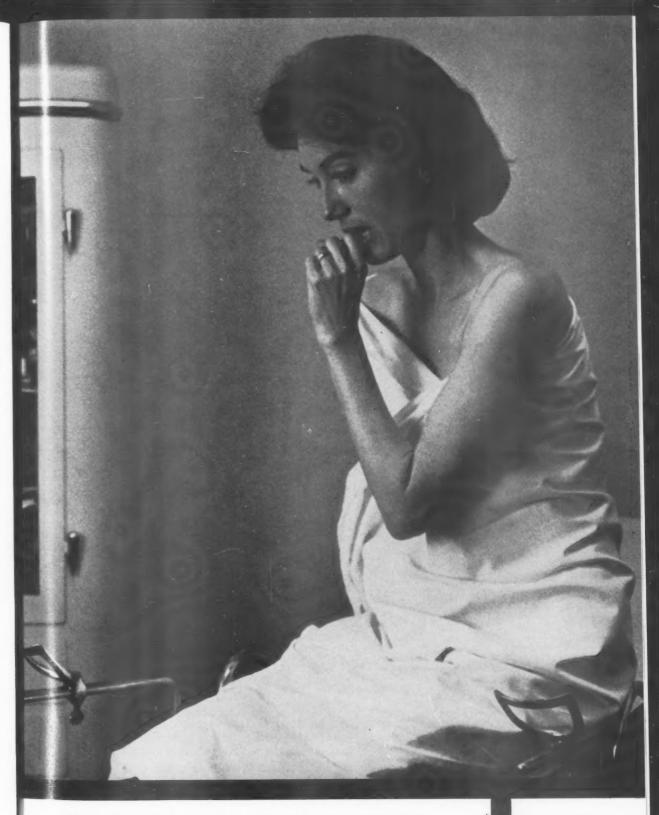
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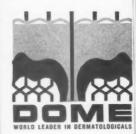
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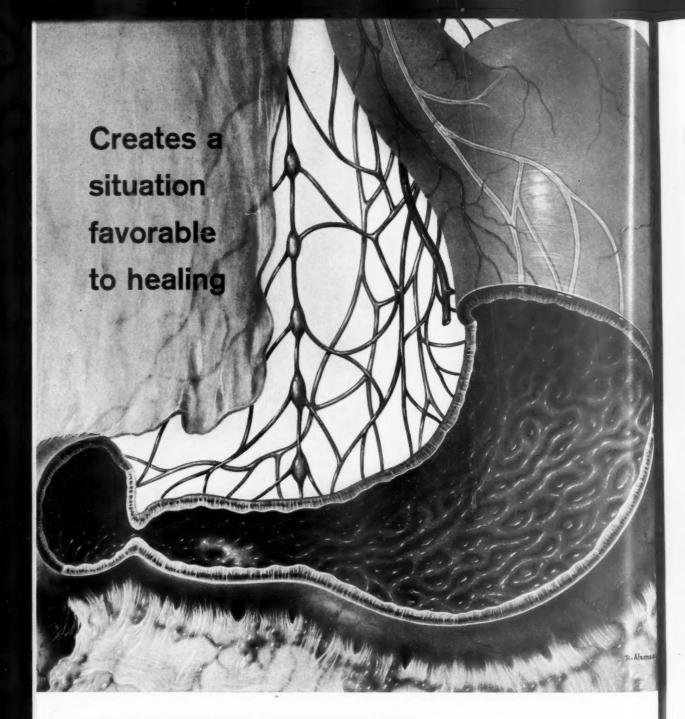
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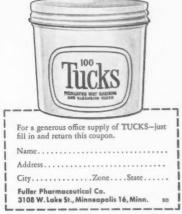
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but certainly not as a toilet wipe when anal areas are sensitive. Unlike harsh, dry wood pulp toilet papers, Tucks are soft cotton flannel pads mildly medicated with witch hazel (50%) and glycerin (10%). Tucks are ideal for routine toilet care when treating pruritus ani et vulvae, diaper rash, hemorrhoids, following episiotomy or hemorrhoidectomy, and in other anorectal conditions. Tucks cleansing, mildly astringent action hastens healing and helps assure patient comfort. Tucks are available at busy prescription pharmacies everywhere in jars of 40 and 100.





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More rapid results more comfortably

In ante- and postpartum use—Fleet Enema provides rapid, thorough action in minutes...yet patients find it much more

comfortable than soapsuds. Insertion is easy and safe because of the pre-lubricated, anatomically correct 2-inch rectal tube. Time saved with Fleet Enema permits "rapid multiparas" to be medicated earlier. 1,2

Fleet Enema can be used with confidence for a variety of diagnostic and therapeutic purposes—even for patients on sodium-restricted regimens.3 Systemic absorption is negligible.

100 cc. contains: 16 Gm. sodium biphosphate and 6 Gm. sodium phosphate in 4½-fl.oz. squeeze bottle.

Pediatric size, 21/4 fl.oz.

Also available: Fleet Oil Retention Enema, 41/4-fl.oz. ready-to-use unit containing Mineral Oil U.S.P.

1. Rosenfield, H. H., et al.: Obst. & Gynec. 11:222, 1958. 2. Bookmiller, M. M., and Bowen, G. L.: Textbook of Obstetrics and Obstetric Nursing, ed. 3, Philadelphia, Saunders, 1958, p. 314. 3. Hellman, L. D.: Gastroenterology.

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The Clinical Study: A "double blind" investigation to evaluate Desoxyn as an aid in controlling weight during pregnancy.

The Patients: 60 pregnant women divided into two groups. One group received Desoxyn each morning, while the other received a placebo of identical appearance.

The Dosage: 10 mg. of Desoxyn Gradumet, orally, once daily, in the morning.

The Clinical Result: The 30 patients taking Desoxyn gained an average of .302 pounds per week for an average of 15 weeks. Of these patients, eight gained no weight at all.

The women taking the placebo gained an average of .534 pounds per week for 16 weeks. Two did not gain.

The Record: During the study, nine of the Desoxyn patients were given diuretics, while 13 of the other women received the same treatment. One patient taking Desoxyn complained of nervousness, while two of the placebo group had the same reaction and reported nausea.

1. Bayly, M. A., Desoxyephedrine As An Aid In Weight Control For Pregnant Clinic Patients, Quart. Bull. Northwestern Univ. M. School, 34:93, 1960.

The Drug:

DESOXYN® Gradumet®

(Methamphetamine Hydrochloride in Long-Release Dose Form*)

All-day appetite control from a single oral dose—5, 10 or 15 mg.

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is dedicated to saving lives from cancer and spearheads the fight against cancer quackery. Its Committee on New or Unproved Methods of Treatment of Cancer has a membership of physicians, lawyers, educators, and public relations specialists. This committee has been a prime mover in developing constructive action

against cancer quackery

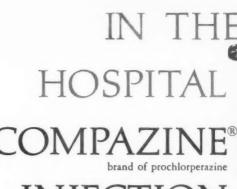
Inspired by model legislation formulated by this committee with the active cooperation of the California Medical Association, California, Kentucky and Nevada recently passed bills providing the first effective means of fighting cancer quackery at its base of operations—in the local community.

To keep both the public and the medical profession informed, the Society has established, in its national office, a central repository of material on new or unproved methods of cancer diagnosis, treatment and cure—a principal source of such information in this country.

The American Cancer Society, in this as in all its efforts, serves both the private citizen and the practicing physician—and is, in turn, served by both.



THE AMERICAN CANCER SOCIETY



INJECTION 5 mg./cc.

To stop nausea and vomiting

In surgery, labor and delivery, and painful diagnostic procedures, 'Compazine' can stop nausea and vomiting, regardless of when it occurs. Krumperman¹ (Temple University Hospital) gave 'Compazine' intravenously to a group of 84 patients with postoperative vomiting. Within 15 to 30 minutes, nausea and vomiting were completely controlled in 68 of the patients. In 14 of the remaining 16 patients, vomiting was completely controlled when a second dose was given 30 minutes after the first.

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Quieter patients with fewer problems for the surgical team and the nursing staff result from treatment with 'Compazine' for anxiety. In the study cited, Krumperman treated 29 patients for anxiety during and after surgery, with 83% good to excellent results.

N.B.: For complete information on dosage, cautions, contraindications and side effects such as occasional neuromuscular reactions (extrapyramidal symptoms) see: Compazine® Reference Manual, Physicians' Desk Reference, or your SK&F representative. Full information is also on file with your pharmacist.

 Krumperman, L.W.: The Use of Prochlorperazine in Anesthesiology, in Clinical Uses of Prochlorperazine (Compazine®), Philadelphia, 1958, p. 82.

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Physicians know that in every pint of blood lie vital hidden treasures.

The AMERICAN RED CROSS knows this, too. Through the Blood Program, licensed by the National Institutes of Health, it provides

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Encourage donors to expand the availability of life's most precious fluid by giving blood wherever there are facilities for receiving it.

In hysterosalpingography "Ethiodol is the drug of choice, both from a diagnostic and a therapeutic point of view" 1

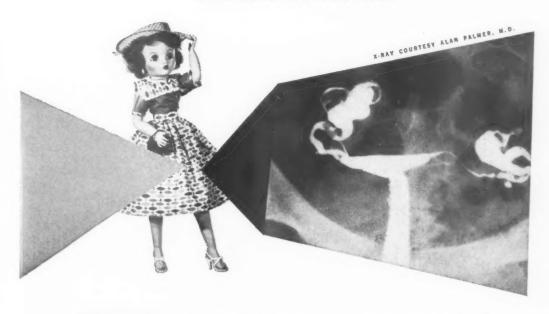
In a recent clinical study, the marked increase in pregnancy success rate demonstrates "the therapeutic superiority of Ethiodol hysterosalpingography over hysterosalpingography with other radiopaque media or carbon dioxide insufflation in the treatment of infertility."²

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Ethiodol brand of ethiodized oil, is the ethyl ester of the iodized fatty acids of poppy seed oil, containing 37% iodine. It is available in 10 cc. ampules, boxes of two. A development of Guerbet Laboratories. Bibliography: 1. Finegold, Wilfred J.: Internat. J. of Fertil. 3:143 1958

2. Palmer, A.: Internat. J. of Fertil. 4:365 1959



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Fosfree Tablets aid in the management, prevention, and control of these "Problems of Pregnancy"

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with cod liver oil

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a suppository, such as **Desitin**, reduces straining at the stool by lubricating the anal canal.¹



conservative treatment is indicated¹⁻³ for mild to moderate symptoms of simple hemorrhoids, fissures, cryptitis, pruritus ani...in pregnant and other patients.

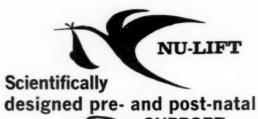
DESITIN SUPPOSITORIES lubricate, soothe, protect, ease pain, itching... and aid healing (with Norwegian cod liver oil, rich in vitamins A and D and unsaturated fatty acids). Free from drugs which might mask serious rectal disease.

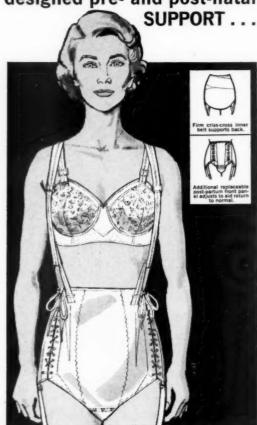
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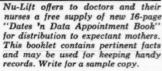
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The acute symptoms of vaginal trichomoniasis—profuse, scalding leukorrhea, itching, swelling, and painful, difficult coitus²—often turn a happy, efficient wife and mother into the family storm center.

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Vagisec explodes trichomonads within 15 seconds of contact

Excellent long-term results by strictest cure criterion

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—lessens "psycho-social"⁵ symptoms, too



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Most physicians advise the use of a prophylactic during coitus, while the wife is under treatment and for four to nine months thereafter; 1,4,6 and when they do, 50.3% specify RAMSES.

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References: 1. Decker, A.: New York J. Med. 57:2237 (July 1) 1957. 2. Karnaky, K. J.: South. M. J. 51:925 (July) 1958. 3. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. 76:666 (Sept.) 1958. 4. Roberts, C. L., and Sullivan, J. J.: West. Med. 1:12 (Apr.) 1960. 5. Trussell, R. E.: New York Med. 13:717 (Sept. 20) 1957. 6. Weiner, H. H.: Clin. Med. 5:25 (Jan.) 1958.

Active ingredients: Polyoxyethylene nonyl phenol, Sodium ethylene diamine tetra-acetate, Sodium dioctyl sulfosuccinate.

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You can see for yourself the efficient detergent action of Trichotine solution in reducing promptly a cervical plug (using a saturated cotton pledget), or washing away the "cheesy" exudate of monilia.

TRICHOTINE is just as effective for therapeutic irrigation by your patient at home

The same qualities — detergency, antisepsis, healing — make Trichotine ideal for the treatment of cervico-vaginitis and leukorrheas, alone or in conjunction with other antimicrobials. In the itching, burning, and foul odor of non-specific vaginitis and leukorrhea the action of Trichotine is immediate and gratifying to the patient.

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Low Dosage - Economical Therapy

Suggested dosage: One tablet three times daily until symptoms are controlled. Thereafter reduce to maintenance dosage of one tablet every day or two, as may be required.

1. N.N.R., 1959, 515; 2. Ibid., 376

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Capillary protective measures in pregnancy

Prenatal treatment and threatened abortion

During pregnancy, fragile capillaries, increased capillary permeability, decidual bleeding, and the tendency toward edema are well recognized. Essential capillary protective factors are an integral part of the prenatal regimen.

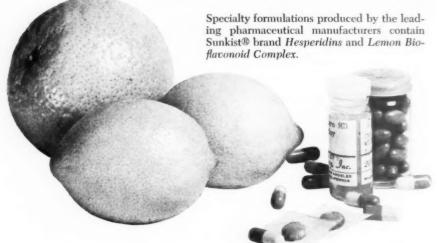
The inclusion of Hesperidin or other citrus bioflavonoids as a "precautionary measure" in every pregnancy and as an "essential measure" in habitual aborters insures the restoration and maintenance of capillary integrity and helps prevent spontaneous abortion.

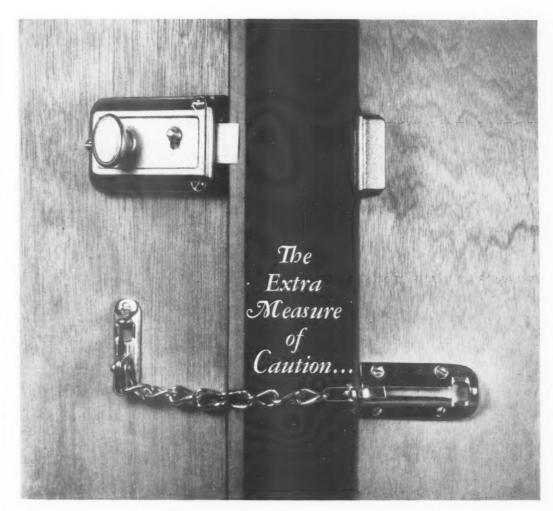
The rationale of Hespiridin and other citrus bioflavonoids — in conjunction with vitamin C, nutritional factors and other therapeutic measures — as adjuncts, is based on the premise that capillary involvement may be a contributing factor in spontaneous abortion and erythroblastosis fetalis.

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SQUIBB Squibb Quality - the Priceless Ingredient

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DECLOMYCIN Demethylchlortetracycline attains—usually within two hours—blood levels more than adequate to suppress susceptible pathogens—on daily dosages substantially lower than those required to elicit antibiotic activity of comparable intensity with other tetracyclines. The average, effective, adult daily dose of other tetracyclines is 1 Gm. With DECLOMYCIN, it is only 600 mg.

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DECLOMYCIN Demethylchlortetracycline sustains, through the entire therapeutic course, the high activity levels needed to control the primary infection and to check secondary infection at the original—or at another—site. This combined action is usually sustained without the pronounced hour-to-hour, dose-to-dose, peak-and-valley fluctuations which characterize other tetracyclines.

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CAPSULES, 150 mg., bottles of 16 and 100. **Dosage:** Average infections—1 capsule four times daily. Severe infections—Initial dose of 2 capsules, then 1 capsule every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper. **Dosage:** 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into 4 doses.

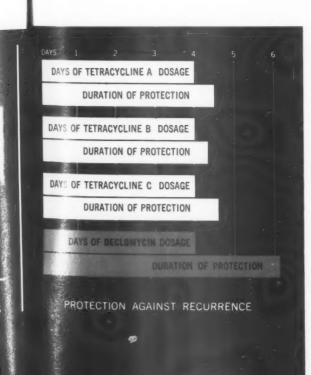
SYRUP, 75 mg./5 cc. teaspoonful (cherry-flavored), bottles of 2 and 16 fl. oz. **Dosage**: 3 to 6 mg. per pound body weight per day—divided into 4 doses.

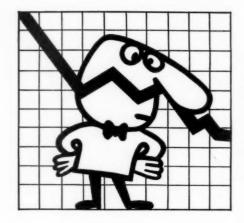
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In relation to "real income," drug prices have actually declined in recent years. At prevailing wages in 1929, it took 91 minutes of working time to pay for the average prescription. Only 86 minutes of labor paid for the average prescription in 1958. As one economist put it, "If the retail prices of drugs had risen as much as the consumer price index since 1939, it would cost the consumer at least an additional one billion dollars to buy the drug preparations now consumed." He goes on to compare the \$19.02 per capita drug expenditure in 1958 with the \$37.19 spent on tobacco products and \$53.72 for alcoholic beverages. When your patients inquire about the cost of medication, perhaps these facts will be helpful in explaining that today's prescription, averaging about \$3.00, is a relatively modest

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"Of considerable benefit to patients whose main symptoms were headache, cramps, depression and lethargy."

J. Am. M. Women's A. 14:415 (May) 1959.

Analgesic



When the pain is unusually severe, prescribe 'EDRISAL with CODEINE' (1/4 gr. or 1/2 gr.).

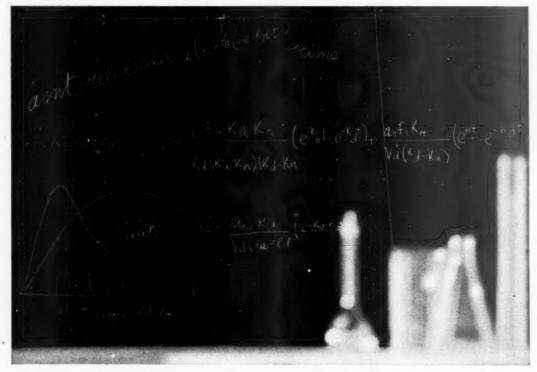
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Indicated in obesity and in psychosomatic complaints. Usual all-day dosage is one Desbutal Gradumet. In two strengths, Desbutal 10 Gradumet (10 mg. of Desoxyn and 60 mg. of Nembutal) and Desbutal 15 Gradumet (15 mg. of Desoxyn and 90 mg. of Nembutal). Desbutal is available at your nearest pharmacy.

in obesity, in psychosomatic complaints

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*DESOXYN-METHAMPHETAMINE HYDROCHLORIDE, ABBOTT. *NEMBUTAL-PENTOBARBITAL, ABBOTT. *GRADUMET-LONG-RELEASE DOSE FORM, ABBOTT; PAT. APPLIED FOR.

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in female urethritis referred pain complicates diagnosis



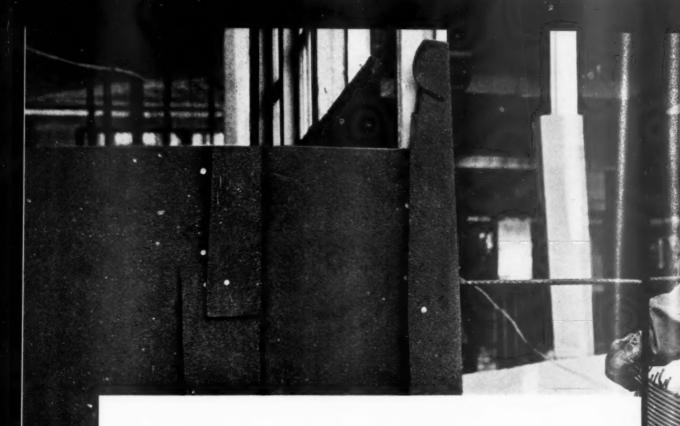
Pain in the groin, suprapubic region, thighs and lower back is often caused by urethritis but, as a result of negative urinary findings, is attributed to other organs. Direct examination of the urethra helps localize the origin of referred pain, evidence of urethral inflammationcalling for local therapy.

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FURACIN® INSERTS and brand of nitrofurazone FURESTROL® SUPPOSITORIES alleviate pain—simplify treatment

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Soma is unique because it combines the properties of an effective muscle relaxant and an independent analgesic in a single drug. Unlike most other muscle relaxants, which can only relax muscle tension, Soma attacks both phases of the pain-spasm cycle at the same time.

Thus with Soma, you can break up both

pain and spasm fast, effectively . . . he give your patient the two things he wan most: relief from pain and rapid return full activity.

Soma is notably safe. Side effects are ra Drowsiness may occur, but usually only w higher dosages. Soma is available in 350 m tablets. Usual dosage is 1 tablet q.i.d.

The muscle relaxant with an independent pain-relieving action





Wallace Laboratories, Cranbury, New Jersey



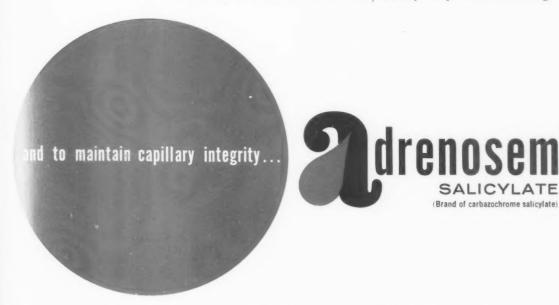


Holding blood loss to a minimum is a medical precept. Clinical studies show that lack of capillary integrity causes abnormal bleeding four times as often as coagulation defects.^{1,2}

Adrenosem aids capillary integrity by decreasing excessive capillary permeability and promoting retraction of severed capillary ends.

Adrenosem protects against bleeding from PREOPERATIVELY small vessels, thus assuring a clearer operative field and minimizing the need for transfusions.

POSTOPERATIVELY Adrenosem reduces postoperative bleeding.



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Supplied: Ampuls, 5 mg. (1 cc.) and 10 mg. (2 cc.) for I.M. injection; Tablets, 1 and 2.5 mg.; Syrup, 2.5 mg./5 cc. (1 tsp.)

- 1. Haden, R.L., et al.: Ann. N.Y. Acad. Sc. 49:641 (May 11) 1948.
- 2. Cheraskin, E.: J. Am. Dent. Assn. 58:17 (April) 1959.
- *U.S. Pat. Nos. 2581850; 2506294

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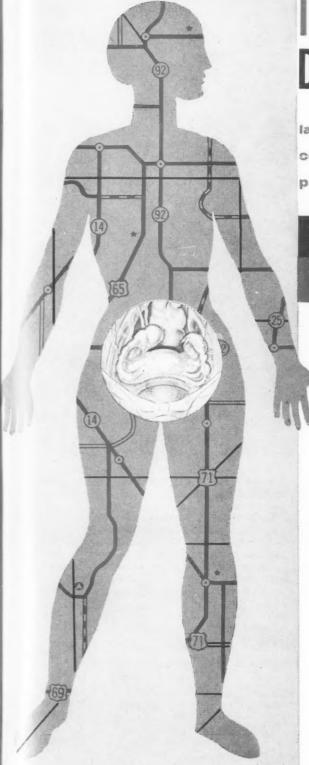
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1. Randall, L. M. 2. Reich, W. J., Rubenstein, M. W., Nechtow, M. J., and Reich, J. B. (literature available on request).

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1. Reich, W. J., and Nechtow, M. J.: Am. Pract. & Digest Treat. 11:45, 1960. 2. Reich, W. J., and Nechtow, M. J.: Scientific Exhibit, Chicago Med. Soc. (March) 1960.

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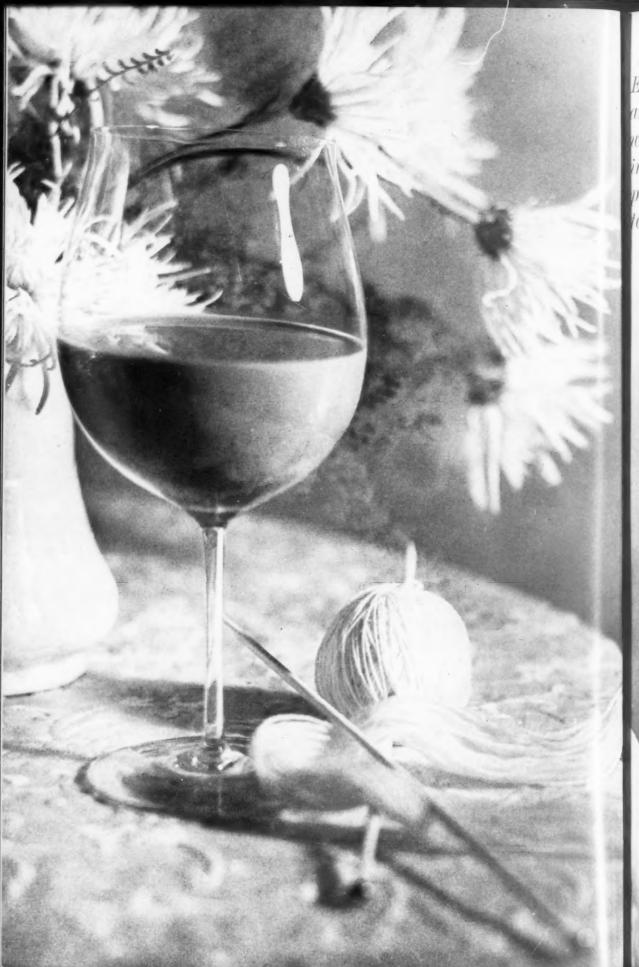
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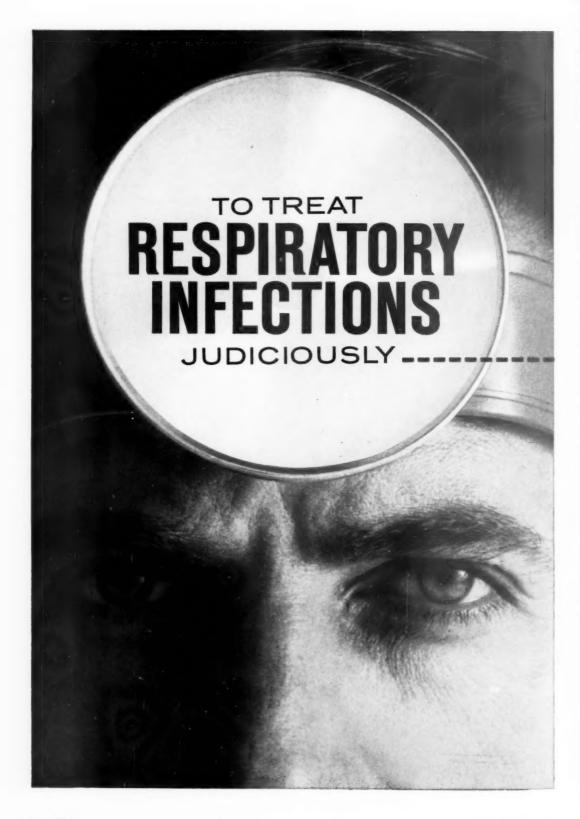
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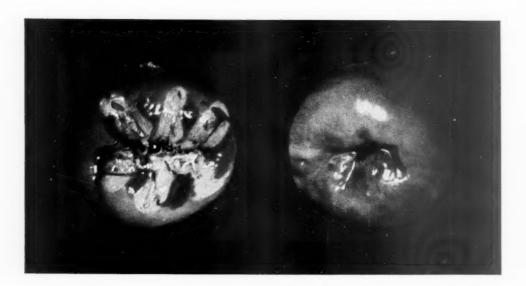
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References: 1. Pitts, R. F., Am. J. Med., 24:745, 1958. 2. Ford, R. V., Cur. Therap. Res., 2:51, 1960.

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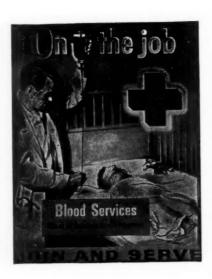
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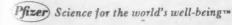
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THE RECOMMENDED DAILY DOSES PRODUCE THIS MUCH GAS - BUT NOT THE PRECALCINS—These balloons dramatically demonstrate the amount of carbon dioxide gas released when the recommended daily doses of six of today's most frequently prescribed prenatal supplements are dropped into simulated gastric juice. The outstanding exception seen here is PRECALCIN which, like PRECALCIN LACTATE and PRECALCIN-D, produces no gas. The reason is simple: All three PRECALCINS contain well-tolerated, gas-free sources of calcium — as lactate and/or phosphate - while the other five supplements contain calcium carbonate. When the carbonate salt reacts with gastric juice (CaCO3 +2HCI→ CO2↑+CaCl2↓ +H2O), carbon dioxide is liberated-both in the test tube and in the stomach. So avoid such gaseous discomforts of pregnancy. Prescribe the PRECALCINS.

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Just
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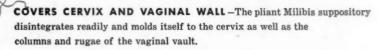
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A welcome clinical advance... effective medication in an appealing form



Soft and pliant as tampon, the Milibis vaginal suppository offers proved therapeutic action* in a vehicle giving unusual clinical advantages to both patients and physician.



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*97 per cent effective in a study of 564 cases; 94 per cent effective in a series of 510 cases.

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